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RESEARCH TRENDS IN LIFE SCIENCE

VOLUME IV

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PREFACE

In the vast expanse of the scientific realm, the field of Life Science stands as a beacon of curiosity, continually illuminating the mysteries of existence. As we embark on a journey through the pages of "Research Trends in Life Science," we find ourselves in the midst of a dynamic and ever-evolving landscape, where the boundaries of what we know are constantly pushed, reshaped, and expanded.

This compilation serves as a testament to the relentless pursuit of knowledge within the Life Sciences—a multidisciplinary domain that spans from the microscopic intricacies of cellular processes to the grand tapestry of ecosystems. Our exploration delves into the forefront of scientific inquiry, where researchers, scholars, and visionaries collaborate to unravel the complexities of life itself.

Within these pages, you will encounter a diverse tapestry of research trends, each thread weaving a narrative of discovery and innovation. From cutting-edge advancements in genomics and biotechnology to profound insights into ecological dynamics, this book encapsulates the pulse of contemporary Life Science research.

As we navigate through the chapters, we invite you to witness the convergence of traditional wisdom and modern methodologies, where technology and tradition dance in harmony to reveal the secrets of the living world. The preface sets the stage for a compelling odyssey, inviting readers to engage with the unfolding stories of breakthroughs, challenges, and the relentless pursuit of understanding life in all its forms.

Embark with us on this intellectual expedition, where the boundaries between the known and the unknown blur, and the pursuit of knowledge becomes a shared endeavor that transcends disciplinary confines. "Research Trends in Life Science" beckons you to join the exploration of the frontiers of life, where every discovery is a stepping stone toward a more profound comprehension of the intricate web of existence.

Editors

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THERAPEUTIC POTENTIAL OF GRAPE SEED OIL

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Abstract:

Grape seed oil, derived from the seeds of grapes, has gained significant attention in recent years for its potential therapeutic benefits. This natural product is rich in polyphenols, antioxidants, and essential fatty acids, making it a valuable resource for various health and wellness applications. This abstract explores the therapeutic benefits of grape seed oil, focusing on its antioxidant properties, potential cardiovascular benefits, skin and hair care applications, and anti-inflammatory effects. Additionally, we discuss the oil's potential in the management of chronic diseases such as diabetes and its role in promoting overall well-being. The research suggests that grape seed oil can be a versatile and beneficial addition to one's daily regimen, offering a wide range of health advantages. However, further studies are needed to comprehensively understand its mechanisms of action and optimal usage for various health conditions.

Keywords: Grape Seed Oil; *Vitis vinifera* L.; Phytochemistry; Bioactive Compounds; Biological Activity

Introduction:

Significant agricultural and industrial waste and byproducts are generated during grape processing, amounting to over 0.3 kg of solid waste for every kilogram of grapes crushed. Grape seeds, comprising 7-20% of processed grapes, are commonly found in pomace and can be easily separated from the skins and fruit tissues. These seeds contain high levels of bioactive antioxidants, making them valuable raw materials for the production of natural extracts, cosmetics, pharmaceuticals, and new food products. The extraction of grape seed oil (GSO) not only contributes to more efficient waste management

but also enhances the economic and environmental sustainability of the grape processing industry.

Grape seed oil, obtained from grape seeds, has been employed in the cosmetic and pharmaceutical industries due to its therapeutic and cosmetic benefits for skin health. GSO primarily consists of triglycerides and unsaponifiable materials. Fatty acids and glycerol form these triglycerides, and the fatty acids can be categorized into saturated, mono-, and polyunsaturated groups based on their double bond content. GSO also contains unsaponifiable constituents such as carotenoids, phytosterols, squalene, phenols, and vitamin E. The quality of vegetable oils, including GSO, is often preserved by using methods like CO_2 extraction and cold pressing, without further refining, to prevent temperature and oxidation-related changes and eliminate solvent residuals (1).

The effects of vegetable oils on the skin depend on their unsaponifiable components, triglycerides, and fatty acids. While scientific understanding of the precise mechanisms and range of cutaneous effects is still evolving, recent clinical research supports the use of vegetable oils in cosmetic science, medicine, and pharmacy. Essential fatty acids, such as linoleic acid (LA) and α-linolenic acid (ALA), play a vital role in skin health, as they cannot be synthesized by the body and must be obtained through diet. Omega-3 (ω-3) and omega-6 (ω-6) fatty acids are subgroups of polyunsaturated fatty acids (PUFAs). LA, found in high concentrations in plant seeds, belongs to the ω-6 family, while ALA is an ω-3 PUFA. The effects of PUFAs in the body are influenced by their interplay, and while ω-6 PUFAs like LA can promote inflammation, they also have anti-inflammatory properties, especially in vascular endothelium. Vegetable oils rich in PUFAs, particularly ω-3 PUFAs, are valued for their potential to prevent and treat various inflammatory conditions, including skin diseases like psoriasis, atopic dermatitis (AD), and acne (2).

Unsaponifiable compounds in vegetable oils, including GSO, have been less studied than their triglyceride content. Flavonoids, phytosterols, phenolic acids, tocotrienols, tocopherols, and carotenoids are some of the unsaponifiable substances found in GSO, and they possess various skin benefits, such as anti-inflammatory, anti-acne, anti-dermatitis, moisturizing, regenerative, anti-wrinkle, and photoprotective effects. Antioxidant activity in GSO is associated with its vitamin E content, and this can vary depending on factors like the cultivation area, soil properties, climate, maturation stage, and harvesting methods. The unique fatty acid profiles and beneficial components in vegetable oils have led to increased consumer interest in improving dietary choices. The search for new drugs from plant

secondary metabolites has gained attention, and GSO, with its biologically active components, holds promise for medical applications.

Botanical and taxonomical description of *Vitis vinifera* l.

Vitis vinifera L. is a creeping species that can attain a height of 12 to 15 meters. Its taproot can reach depths of 2 to 5 meters and, in some cases, even extend to 12–15 meters or more. The vine exhibits flaky bark, and its stems grow by extending from their tips. As they mature, these stems become woody branches that can grow to significant lengths. Each branch consists of multiple segments separated by nodes, where leaves, flowers, and tendrils develop. The leaves are arranged alternately, palmately lobed, and typically have three to five pointed lobes. They are characterized by a glossy dark green upper surface and a lighter green underside. The flowers of *Vitis vinifera* are small and range in color from greenish to white. They are grouped in inflorescences. The calyx is composed of a single sepal with five short teeth, while the corolla comprises five petals fused at their base. Each of the five stamens is equipped with glands. The ovary is positioned above and features a short style with a button-shaped stigma.

The fruits of *Vitis vinifera* vary in shape depending on the subspecies, but they are generally berries, commonly referred to as grapes. These grapes typically have an ovoid or globose shape and come in dark blue or greenish colors, reaching sizes of up to 3 centimeters in diameter. Unripe grapes are typically green, while ripe grapes take on a dark purple hue. When fully mature, grapes turn grey. The seeds of these grapes are pear-shaped, dark brown in color, have a smooth surface with ridges on the back, and a discoidal apex. They measure between 4 to 8 millimeters in length and have a bitter taste (3).

Therapeutic effects of grape seed oil

On exploring the biological effects of grape seed oil, which has gained attention due to its various bioactive components. GSO is considered a valuable dietary supplement that could potentially aid in preventing or managing physiological abnormalities associated with chronic illnesses. However, several key questions remain unanswered, such as optimal dosage, bioavailability, and potential side effects in humans. To better understand its physiological functions, it's essential to examine the specific oil components found in the available literature, particularly those related to the extraction methods. In the field of cosmetology, GSO is used as a raw material and is known for its soothing, softening, antioxidant, and normalizing properties. GSO is recognized for its positive impact on health due to its content of fat-soluble vitamins, polyunsaturated fatty acids (PUFAs), and various

antioxidants, including carotenoids, polyphenolic compounds, and tocopherols, which exhibit anti-inflammatory, antibacterial, and antioxidant properties (4).

Traditional uses

Historical evidence supporting the use of *Vitis vinifera* L. for its healing properties can be found in written (e.g., cuneiforms, epigraphs, papyri, manuscripts) and visual sources (e.g., frescoes, murals, vase paintings, sculptures, iconography, mosaics, miniatures). The cultivation and wine-making techniques related to grape varieties are mentioned in ancient texts, such as the works of Homer, Virgil, and Horace. The Old Testament also references the planting of a vine by Noah after the great flood. In ancient China, fermented grape drinks were reportedly used as early as 7000 BC. Papyrus and ceramic fragments containing mentions of *Vitis vinifera* L. have been discovered, and it's evident that grapes were considered essential for good health in various mythologies and religious writings, even in the Americas before the arrival of explorers and missionaries. *Vitis vinifera* L. has been a part of the traditional Indian Ayurvedic system of medicine for therapeutic purposes for centuries (5).

Anti-hypercholesterolemic and cardioprotective effects

Grape seed oils are rich in polyunsaturated fatty acids (PUFAs) and phytosterols, which can be beneficial for cardiovascular and metabolic health. The primary unsaturated fatty acid in grape oil is linoleic acid (LA), known to support heart health. Additionally, cold-pressed GSO contains compounds like quercetin, ethyl gallate, and ethyl caffeate, which have shown inhibitory effects on the enzyme protein tyrosine phosphatase 1B (PTP-1B) and may be beneficial in managing type 2 diabetes. Phytosterols, such as stigmasterol, β-sitosterol, and campesterol, found in grape oil, have minor lipophilic compounds with potential health benefits related to antioxidant properties and their impact on cholesterol metabolism. Consuming berries, which include GSO, can help maintain a healthy gut microbiome and potentially improve plasma lipid profiles in humans, thus reducing the risk of cardiovascular disease. Studies have shown that supplementing with GSO significantly reduces triglycerides and LDL-cholesterol levels in rats with high-fat diets, which is used to manage hyperlipidemia (6).

Antioxidant potential of GSO

Assessing the antioxidant properties of plant materials is a primary focus of research due to their high antioxidant content, which is associated with health benefits. Multiple methods have been developed to measure antioxidant levels in beverages and

foods, but there is no universally agreed-upon gold standard technique. This lack of consensus is due to various methodological limitations, such as the challenge of determining the hydrophobic or hydrophilic nature of antioxidants and difficulties in defining the reaction endpoint. The antioxidant properties of grape seed oil are attributed to the presence of both lipophilic and hydrophilic compounds in its composition. Specifically, the high content of a vitamin E isomer, namely α-tocotrienol, which is relatively rare in other oils, is closely linked to the antioxidant activity of GSO, as supported by existing literature. Research has shown that tocotrienol-rich fractions possess antioxidant and anti-tumor properties. Tocotrienols, particularly in reducing iNOS and inhibiting COx-2, exhibit superior antioxidant potential compared to other tocopherol isomers. Additionally, tocotrienols are known to enhance insulin sensitivity, which may contribute to GSO's potential anti-inflammatory and antioxidant effects. In a study conducted by researchers, the antioxidant activity of GSO from red and white grape varieties was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,20-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. Their findings indicated that the highest antioxidant capacity was obtained from GSO extracted from red grapes using supercritical fluid extraction (7).

Wound healing effect

Fatty acid constituents in vegetable oils, especially polyunsaturated fatty acids like linoleic acid (LA), are believed to play a significant role in the wound-healing process. Oils with a higher ratio of linoleic acid to oleic acid have shown greater efficiency in restoring lipid barriers. Further comprehensive research is needed to gain a deeper understanding of how vegetable oils affect the skin and vice versa. Components such as carotenoids, polyphenols, sterols, and vitamin E in GSO have been found to reduce the negative effects of free radicals and support the synthesis of collagen, thus promoting wound healing. Vitamin E's humectant properties on skin wound scarring have also been demonstrated. Sterols are effective substances that can aid in reducing systemic inflammation and accelerate the formation of new skin by activating macrophages and boosting fibroblast and collagen production. Additionally, a synergy between grape oil, which contains 20.10 ± 0.02 mg/g hydroxyproline, and its wound-healing and antibacterial functions have been suggested, resulting in a substantial reduction in wound area following grape oil administration. It was indicated that grape skin also has wound-healing properties, with wound areas being healed on the 13th day (8).

Antimicrobial effect

Numerous research studies have focused on grape pomace, particularly grape seed extracts (GSE), and their antimicrobial properties. Previous research suggests that Gram-positive bacteria are more susceptible to GSE compared to Gram-negative bacteria, possibly due to the structural differences in their cell membranes.

To analyze the chemical profiles of seed oils from different Serbian white grape varieties and assess their efficiency in terms of antioxidant and antibacterial properties. In terms of antimicrobial activity, GSOs obtained through Soxhlet extraction demonstrated antibacterial effects against Staphylococcus aureus*, E. coli, B. subtilis, E. faecalis,* and *K. pneumoniae*, while other bacteria remained unaffected by GSO. Fatty acids are believed to contribute to this antibacterial action by functioning as anionic surfactants, especially at lower pH levels. They can also increase the permeability of bacterial cell membranes by integrating their hydrocarbon chains. Polyphenols have been shown to be effective against Gram-positive bacteria by targeting various bacterial structures, including cell walls, membrane receptors, lipid membranes, ion channels, biofilm formation, and bacterial metabolites. Other components, such as α-tocopherol, have been reported to be more effective against Gram-positive than Gram-negative bacteria. It was investigated the antibacterial effects of grape seed and blackberry extracts obtained through Soxhlet extraction against Staphylococcus aureus and Escherichia coli, with only non-polar extracts showing inhibitory effects (9).

Cosmetic use

Various grape extracts can be incorporated into cosmetics and personal care products, including extracts from the fruit, leaves, flowers, seeds, roots, and other plant parts. These extracts are utilized for their potential benefits in skincare and cosmetic formulations. The Cosmetic Ingredient Review (CIR) Expert Panel has previously assessed the safety of grape seed oil and hydrogenated grapeseed oil for cosmetic use and determined that these compounds pose no risks when used in cosmetics (10).

Grape seed oil is beneficial for cosmetic and personal care applications due to its fatty acid (FA) content. Linoleic acid (LA), an essential fatty acid that cannot be produced by the human body, is particularly valuable. A deficiency in LA can lead to dry skin, hair loss, brittle nails, and increased trans-epidermal water loss. LA is commonly used in cosmetic products to effectively address issues such as acne vulgaris, dermatoses, and sunburns. Grape seed oil contains high concentrations of phenolic compounds and

unsaturated fatty acids, making it a valuable ingredient for skincare products. The antioxidants in grape seeds help enhance cellular resilience and protect fibroblasts from UV damage, making them valuable in cosmetic formulations. Some sunscreen products incorporate grape extracts with anti-inflammatory properties to reduce UVB-induced erythema or boost the sun protection factor (SPF) (11).

Grapes offer a range of beneficial compounds for cosmetic products. Phenolic compounds, such as proanthocyanidins, gallic acid, caffeic acid, and ferulic acid, along with flavonoids, serve as effective antioxidants and are essential in the development of post-sun skincare products used in cosmetic surgery. Grapes also contain phenolic substances like catechin, anthocyanins, and various fatty acids, which counteract signs of epidermal aging and slow down the process of photoaging. The natural antioxidant content of grapes enhances the sun protection factor (SPF) and photostability of sunscreens. Research has shown the advantages of applying and consuming polyphenols from various plant species, including Vitis vinifera, for protection against UV radiation. These properties make grapes a valuable component in cosmetic products designed to protect and enhance skin health (12).

Conclusion:

In conclusion, grape seed oil has emerged as a promising natural product with a multitude of potential therapeutic benefits. Its rich content of polyphenols, antioxidants, and essential fatty acids make it a valuable resource for promoting health and wellness in various ways. The antioxidant properties of grape seed oil can help combat oxidative stress, potentially reducing the risk of chronic diseases and supporting overall well-being. Its potential cardiovascular benefits, including its role in managing diabetes, further highlight its positive impact on health. Grape seed oil's applications in skincare and haircare underscore its versatility, offering a natural and nourishing option for personal care routines. Additionally, its anti-inflammatory effects add to its potential in managing various health conditions. While the existing research suggests the numerous advantages of grape seed oil, further studies are essential to gain a more comprehensive understanding of its mechanisms of action and the optimal ways to incorporate it into different health regimens. With ongoing research and exploration, grape seed oil may continue to reveal even more of its potential in promoting health and enhancing the quality of life.

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BIOLOGICAL EFFECTS OF HAND-HELD MOBILE PHONES ON THE HUMAN BODY – A COMPREHENSIVE REVIEW

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Introduction:

As in the words of the renowned physician, Jennifer Williams, "Oral health is a reflection of the physiological, social and psychological factors that are essential to our quality of life." Oral health is integral to general health so that it contributes to the overall wellbeing of all individuals. Human saliva is not just a fluid in our mouth, but it mirrors our body's health and maintenance.

Saliva helps in digestion, protection, defence, speech and has anti-microbial action. The various salivary compounds can be classified as inorganic, organic, non-protein, protein or polypeptide, enzymes, hormones, lipid molecules and electrolytes and immunoglobulins. Recent years have witnessed an increasing interest in using saliva as a diagnostic tool. Saliva is known for its simplicity and needs a non-invasive collection method. Saliva sampling is safe for the operator and the patient because of its ease in collection and low-cost storage methods. The secretion of saliva is influenced by various external and internal factors and one such important external factor is the radiation. One such important source of radiation in the technologically driven world is the hand-held mobile phone.

The world's culture has seen enormous growth in digital technology with mobile phones being in the forefront. A mobile phone is defined as a telephone with access to the cellular radio system so that it can be used over a wide area without a physical connection to the network.

Out of the seven billion global population, about 62-67% of the population are using mobile phones on a regular basis and an average adult spends 90 minutes a day on their mobile phone. Such is the inevitable role of mobile phones in our rapidly evolving world. Mobile phones work on a specific set of wave energy called the electromagnetic radiation.

Various studies showed an increased risk of malignant gliomas, acoustic neuromas and tumours that occurred on the side of head where the mobile phone is routinely placed. Results like fluctuations in electroencephalograph patterns, sleep patterns, endocrinal dysfunctions, decreased cognitive function and abnormal melatonin secretion has been observed in patients with prolonged mobile phone usage. Considering the location of the parotid salivary gland and its relationship with the placement of the mobile phones, and the fact that it lacks physical protection of any bony structures around it, it is evident that the parotid glands are highly influenced by the mobile phones and their electromagnetic radiation spectrum. These effects are increased in the dominant side of mobile phone placement during the conversations.

The changes in the parotid gland due to the constant exposure to the electromagnetic waves from the mobile phones can be perceived in many ways. The radiations can affect the parasympathetic systems such that there is altered salivary flow rate. Also, there can be a stimulating effect on the secretion of non-storage granules. Fluctuation in the salivary flow rate, changes in the biochemical constituents of parotid saliva like the protein content, amylase, oxidative stress and subsequent enlargement of the gland has been observed in few studies done on mobile phone users.

While the existing evidence-based studies provide little information about the increased risk of tumours in the parotid region due to the use of hand-held mobile phones, the evidence is not enough to completely rule out any possible carcinogenesis as the International Agency for Research on Cancer (IARC) on 31 May 2011, has classified the electromagnetic fields emitted by mobile phones as possible carcinogenic to human (Group 2B).

Biological effects of mobile phones

Various authors have evaluated the effects of the electromagnetic radiation originating from mobile phones on the different biological tissues of the human body. All sources of EMF, as a rule, are a provenance of complex electromagnetic radiation (EMR), which affects plants, animals, insects, and soil flora in the zone of influence of EMF. Their levels in some cases exceed the maximum recorded natural electromagnetic background by 200-30,000 times. Strong deviations of the EMF from the natural level, to a greater or lesser extent, go beyond the limits of the vital activity of living organisms and are a stress factor. EMR generated by mobile communications acquires the role of a permanent source of environmental pollution. The question of the nature of the influence of the EMF on the

human body and its functions remains debatable. Ozguner *et al.* in 2005 conducted a study to investigate the effects of 900 MHz electromagnetic irradiation on the induction of histopathologic changes in skin and the effect on the secretion of melatonin. Thirty male rats were used for the study. The experimental groups were composed of: a nontreated control group, an irradiated group (IR) without Mel and an irradiated with Mel treatment group. They performed histopathologic evaluation and observed that there was increase in the thickness of stratum corneum, with atrophy of epidermis, papillomatosis, basal cell proliferation, increased granular cell layer in epidermis, impairment in collagen tissue distribution and separation of collagen bundles in the dermis. The authors concluded that an exposure to 900 MHz radiation emitted by mobile phones caused mild changes in the skin. The authors concluded that melatonin treatment can reduce these changes and may have a beneficial effect to prevent 900 MHz mobile phone-induced rat skin changes.

Another study was conducted to estimate the accuracy and reproducibility of citric-acid-stimulated parotid saliva sampling. In healthy individuals a strong correlation between flow rates from the left and right parotid gland was observed. In patients with Sjögren's syndrome the correlation was stronger. Increasing the number of collections did not reduce the flow rate variation significantly. In patients who were diagnosed of head and neck cancer, the authors evaluated if repeated parotid saliva measurements provided a reliable baseline value such that it can be used for clinical studies. They observed that repeated collections did not result in a significant reduction of intra patient variation, similar to the results with the healthy volunteers. Thus, the authors concluded that a high variation in parotid flow rates have to be considered when planning clinical trials evaluating the effects of treatment on salivary gland functioning are being carried out. Several studies proved that the EMR radiations had an effect at the cellular level by causing changes in the DNA of the peripheral blood lymphocytes of individuals using mobile phones. Most commonly studies EMR waves were between a wavelength of 800 to 2000MHz. The in vivo capillary blood MNT also revealed highly significant frequency of micro nucleated cells. The authors concluded that a positive correlation was present between mobile phone usage and genetic damage of cells. The possible negative impact of mobile phone radiation on sperm quality has been established recently.

While no certain conclusions can be drawn from current evidence, a growing number of studies indicate a decrease in male fertility associated with cellular phone usage. An excellent study, one of the first on this topic, was presented by Agarwal *et al.* in 2008.

The authors concluded that the use of cell phones by men is associated with a decrease in their semen quality. According to the researchers' data the decrease in sperm count, motility, viability, and normal morphology was related to the duration of exposure to cell phones. Boulos and Hassan, in 2013, concluded that cell phone use in men is associated with decreased semen quality in the form of decreased sperm count, motility, viability and normal morphology, which depend on the duration of cell phone exposure time. The authors found a significant positive correlation between the decrease in the different sperm parameters: the decrease in the value of one of these parameters is concomitant with other parameters changes.

Risk of parotid tumours

Lonn *et al.* (2006) conducted a study among the population of Denmark and Sweden that aimed at testing the effect of long-term mobile phone usage and the risk of parotid gland tumours. The authors identified all cases aged 20-69 years diagnosed with parotid gland tumour and detailed data regarding mobile phone usage was collected from 60 cases of malignant parotid gland tumours. For regular mobile phone users regardless of duration, the risk estimates for malignant and benign tumours were 0.7 and 0.9%. The authors concluded that the increased use of mobile phone did not increase the risk of parotid gland tumours. Sadetzki *et al.* (2014) conducted a study about mobile phone use and the incidence of tumours affecting the parotid gland. The study evaluated about 402 benign cases and 58 malignant cases of parotid gland tumours. No increased risk of parotid tumours was observed in a regular cellular phone user. For ipsilateral use the odds ratio in the highest category of cumulative number of calls and call time without use of hands-free devices were 1.58% and 1.49% respectively. The authors concluded that there was an association between cellular phone usage and parotid gland tumours. Many authors explored the relationship between long-term (>10 years) use of wireless phones and the development of malignant brain tumours. Case control studies were conducted on brain tumour cases of both genders where they observed that the persons who used both the side of ears for speaking over mobile phones were at a lower risk of developing tumours. They hypothesized that radiofrequency electromagnetic radiation plays a role both in the initiation and promotion stages of carcinogenesis.

Yadav and Sharma (2007) evaluated whether mobile phone radiations cause any in vivo effects on the frequency of micronucleated exfoliated cells in the exposed subjects. A total of 109 subjects were included for the study. 85 mobile phone users were considered

as exposed subjects and 24 non-users were considered as controls. Exfoliated cells were obtained from the buccal mucosa using a swab from both the groups. One thousand exfoliated cells were screened from each individual for nuclear anomalies including micronuclei (MN), karyolysis (KL), karyorrhexis (KH), broken egg (BE) and binucleated (BN) cells. Mean frequency of broken egg is found to be more in exposed subjects (0.65+/-0.276) as compared to controls (0.50+/-0.217). Frequency of presence of more than one nucleus in a cell (binucleated) is also higher in exposed (2.72+/-0.374) in comparison to controls (0.67+/-0.231). Thus, the authors concluded that there was a significant increase in micro nucleated cells in mobile phone users compared to normal population. Jatin and Kanupriya performed a study were done to evaluate the changes in salivary flow rate of the parotid glands and assess the adverse effects associated with heavy mobile phone users. A total of 200 participants were divided into three groups depending upon the average hours of mobile usage per day. Unstimulated parotid salivary flow rate was measured from both sides using modified schirmer strips. Lipid peroxidation levels were analysed in which the heavy user group showed significant rate of parotid salivation on the dominant side compared to the non-dominant side in contrast to the control group in which no significance was observed in antioxidant levels.

Goldwein and Aframian performed a study on hand-held mobile phones to evaluate the various physiological changes occurring in the parotid gland in the area of maximum placement of mobile phone usage. The study showed increased salivary secretion in the dominant side of placement of mobile phones. The mean stimulated parotid salivary flow rate measured was almost 1.5 times higher than the secretion rate of the left parotid gland. Overall, the total protein concentration was 1.2-fold higher in the dominant side of usage. Bhargava *et al.* (2012) had evaluated the effect of hand-held mobile phone usage on the salivary flow rate and volume of the parotid gland. The authors selected a total of 142 participants who were segregated into two groups. The former group used hand-held mobile phones for more than 2 hours in a day and the latter group consisted of participants who used mobile phones for less than 2 hours. The authors observed a change in the salivary flow rate which increased in the participants who used mobile phones for more than 2 hours and their parotid volume also increased.

Pattipatti *et al.* in 2015 performed a study to see the changes in the flow rate of saliva and concentration of total proteins in parotid saliva. Parotid saliva was collected from right and left parotid gland of 50 healthy volunteers. There was decrease in the

secretion of saliva on the dominant side and no much changes in the protein concentration between the dominant and non-dominant sides, thus concluding that there were functional changes that were evident in the parotid gland in long term users of cell phones the parotid.

Mobile phone is a wireless hand- held device that allows the users to make and receive calls. The mobile phone technology used widely is the Global system for mobile communication (GSM) and the Code division multiple access (CDMA). The GSM technology and CDMA technology use different band widths to communicate without any interference for long hours. Mobile phones work on the principle of production of electromagnetic radiofrequency signals that are distributed over various wavelengths and help in distance communication. To measure the intensity of these radiofrequency waves and determine the biological effects, a value named specific absorption rate (SAR) is calculated. It is defined as the amount of energy absorbed per unit time per unit mass of tissue. It is expressed in W/kg. The International Commission on Non-ionizing Radiation Protection has set a permissible limit of 2.0W/kg (SAR value) across the globe. Despite strict regulations to control the SAR values by various bodies, the excess usage of the device has increased the speculation about the possible negative impact of mobile phone radiation.

The possible role of cell phone exposure on tumour induction has been reported in various studies till date. In a meta-analysis conducted in 2009 on 23 studies, it was concluded that there was an increased risk of tumours because of radiations emitted from the mobile phones. Dr. Lennart Hardell compiled the results of 16 case control studies and two cohort studies and found that mobile phone users had increased risk of malignant gliomas, acoustic neuromas and tumours. He also observed that the tumours were likely to occur on the side of head where the mobile phone was routinely placed. Later in a separate report, Dr. Lennart Hardell stated that age was a significant factor in the occurrence of tumours. Several studies have highlighted the role of cell phones and its electromagnetic exposure on sperm mobility, morphology and viability and proposed that there can be a reduction in the male reproductive potential. A few reports also suggest that there were variations in the chromosomes with DNA damage seen as abnormalities of micronuclei. Increased thickness of stratum corneum, atrophy of epidermis, basal cell proliferation and impaired collagen distribution were among the other findings seen in the chromosomal level.

Also there are many localised symptoms experienced among the general mobile phone users who complain of fatigue, head ache, decreased concentration, warmth around the ear, tingling sensation and burning sensation in the skin adjacent to the placement of mobile phones, ear pain etc., A number of studies have been carried out wherein preformed questionnaire regarding the adverse effects of cell phone usage was listed and it was found that mobile phones users listed many symptoms that occurred due to prolonged placement of mobile phones over the parotid region.

The possible reason could be because of the heating of the biological tissue leading to modification in the cutaneous blood flow leading to an increase in the perfusion of the tissue. Long term heat exposure can lead to an enriched capillary bed in the parotid parenchyma caused by an increase in blood perfusion and an increase in number of blood vessels in the region. The skin adjacent to the placement of hand-held mobile phones becomes warm due to the transfer of radiation and heat. Hand held mobile phones can generate heat no greater than 0.1 degrees Celsius in the highest-powered models according to Van Leeuwan et al. In our study 60% of participants complained of warm sensation due to prolonged usage. The heating of any biological tissue is due to the absorption of microwave energy by the water content of the tissues. The enriched capillary bed adjacent to the parotid glands cause increased perfusion due to the blood vessel propagation over an extensive time of heat exposure leading to increased salivary flow rate.

Also, the increased salivary flow rate may also be attributed to the secretory parenchymal tissue expansion leading to increase in the entire parotid gland volume, similar to the study conducted by Horowitz and Soskolne. Their study hypothesised that heat exposure given to rats for a period of 28 days can cause changes in the weight of the salivary glands and the size of the salivary glands thus concluding that heat is responsible for structural changes in the salivary gland.

Conclusion:

Hand held mobile phones have created a huge leap in the field of connectivity and communication. It has become a major form of communication that has users ranging from young children to aged individuals. The electromagnetic radiation emitted by the mobile phones and the signals distributed from the base stations are a major concern that can produce a range of health hazards to the individual and the community at large.

Saliva is a diagnostic tool that is a non-invasive and effective screening tool that is gaining a lot of clinical importance. The many organic and inorganic constituents of saliva

play a vital role in determining any pathological changes in the salivary glands and its activity. Earlier studies aimed at analysing the side effects of using mobile phones like production of warmth over the facial region, ear pain, burning sensation over the skin, alterations in salivary flow rates through preformed questionnaires. More emerging studies are aimed at analysing the potential role of mobile phones as a factor for tumorigenesis in the head and neck region. Future studies can be done to evaluate various other biochemical, immunological and mutagenic properties. When the literature is reviewed, we find that not many studies are done in this field especially in relation to the oral cavity and related structures even though they are the closest and most susceptible to any effect which may occur. Moreover, continuation of such researches on the mobile phone radiation effects is needed to assess if these effects could lead to potential long-term harmful consequences. It also helps us to improve the basic reliability of safety standards. Various seminars, discussions, public awareness can be brought about by the tele-health technology education programmes targeting the population with high mobile phone usage.

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TRICLOSAN AND ITS IMPACT ON ENVIRONMENT AND HUMAN HEALTH

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Abstract:

Triclosan (TCS) is an antimicrobial compound and highly toxic to living organisms even at very low concentrations. It is an endocrine disrupter with anti-androgenic and oestrogenic properties and reduces serum level of thyroid hormone. Triclosan were continually discharged into the environment through anthropogenic activities by excretion, washings, manufacturing, etc. and thus, commonly detected in aquatic ecosystems TCS is more frequently detected compound in the environment. TCS in various environmental and biological samples which includes, wastewater, sludge, surface water, sediments, breast milk, human urine, soil, vegetation and groundwater in the range of ng L^{-1} in liquids and ng g^{-1} to mg kg^{-1} in solids. Hence, this chapter explained about toxic effect of triclosan on environment and human health

Keywords: Triclosan-degradation-toxicity-environment-human health

Introduction:

Triclosan (TCS) [5-chloro-2-(2,4- dichlorophenoxy) phenol] is a chlorinated chemical having antimicrobial properties, which was introduced about more than 50 years ago and used as preservatives and antiseptic agent in most of the consumer products, such as soaps, cosmetics, dental products, textiles, toys, paints, furniture and other household products (Sabaliunas *et al.,* 2002) and also it has been categorized as halogenated aromatic hydrocarbon having phenolic, diphenyl ether and polychlorinated biphenyl (PCB) substances (Ahn *et al.,* 2008).

Triclosan was patented for the first time by swiss company – Ciba-Geigy in 1964 (Rolf, 2014a) and registered the TCS as a Pesticide in 1969 and introduced for use in personal care products as antimicrobial agent and preservative by 1970s and it was mainly used as hospital scrub. The application of TCS was expanded commercially from the year 2000 and could be found in 75% and 25% of bar soaps and from 2014, they were used in more than 2000 consumer products up to 0.1- 1.0 % wet wt (Halden, 2014b). At present,

Baden Aniline and Soda Factory (BASF), manufactures TCS under the name of Igrasan DP300 and the structure of Triclosan is given below (Fig.1).

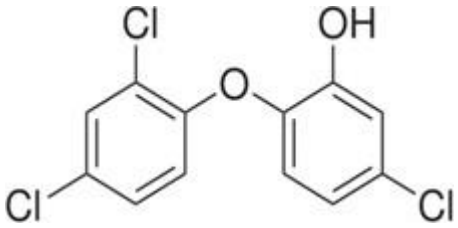

Figure 1: Chemical structure of Triclosan

Antibacterial soaps, detergents contain the triclosan concentrations of 0.1 – 0.3% by weight. The usage of antimicrobial products is steadily increasing in worldwide. Due to their continual usage, triclosan is frequently detected in sewage effluents, biosolids and soils of waste water treatment plants (WWTPs) and also in rivers, lakes and sea water (Kumar *et al.,* 2010). Suddenly it gets transformed into methyl-triclosan and dioxin compounds when it‘s heated. Triclosan bioaccumulates in aquatic plants, animals and poses various ecological risks. Then it also enters into the food chain from contaminated water and agricultural runoff. In soil, sludge and sediments, triclosan is readily degraded in the environment through photodegradation or sunlight irrandiance with a half-life of a week in aerobic and a month to years in anerobic conditions, forming other compounds like, chlorophenols, chloroforms and also dioxins (Latch *et al.,* 2005). In atmosphere, Triclosan has been degraded with a half-life of 8 hours based on the reaction of photochemically produced hydroxyl radicals.

TCS is a widespread environmental contaminant and has been determined in urine, blood, breast milk, amniotic fluid, and so on from the general population in different parts of the world (Nasab *et al.,* 2022; Weber *et al.,* 2022). It is known that humans could be exposed to TCS through dermal contact and direct ingestion whereas in the environment, TCS exposure occurs dominantly via the contaminated water, food, or animals (Milanović *et al.,* 2021)

It is bacteriostatic at low doses and at higher doses, it acts as a bactericidal agent. Triclosan also inhibits fatty acid synthesis in plants and other living organisms. When it enters the cell, it poisons a specific enzyme called enoyl-acyl carrier protein reductase (ENR) preventing bacteria from synthesizing fatty acids required for building their cell membranes. It also has genotoxic and cytotoxic effects in algae and tends to bioaccumulate in algae, fish and enters into food chain (Brain *et al.,* 2008) and it also found to have

synergistic effects when combined with other common contaminants of water, which potentially making triclosan more toxic to environment. Chen *et al*. (2023) suggested that TCS has adverse effects on endocrine function, thyroid hormones and antibiotic resistance. The carcinogenicity of TCS has been studied in rats and mice and indicated that it cause liver pathogenesis, particularly tumour formation with the concentration of 0.25- 0.35 mg L^{-1}.

Degradation products of Triclosan

Methyltriclosan

During wastewater treatment process, the formation of TCS to methyl-triclosan through biological process [MTCS; 5-chloro-2-(2, 4 dichloropheoxy) anisole) and their lipophilicity of methyl-triclosan, resistance to biodegradation and photolysis processes makes the mobilite and exhibit a higher degree of environmental persistence than the parent compound which results in larger the fraction of TCS is transformed to methyl-triclosan. Majority of TCS recovered as methyl-TCS about 16.5 and 50.6 % respectively. The MDL of methyl-triclosan was 0.25 ng g^{-1} in sludge and 1.4 ng g^{-1} in biosolids and the half-life of TCS was determined in 104 days and the methyl-triclosan was more persistent than TCS and was estimated to be 443 days. The slow deterioration of methyl triclosan from the parent compound were measured in fish liver and intestine, methyl-TCS will bioaccumulate upon chronic exposure and posing a potential threat to humans as a result of fish consumption (James *et al.,* 2012).

The Methyl-TCS/TCS ratio can largely exceed in effluent, surface water, sludge, and sediment. Benny *et al*. (2014) showed that the fraction of methyl triclosan can become substantially higher in the environment, where TCS is readily degraded. This transformation of TCS into Methyl-TCS will ultimately increase the environmental persistency of triclosan, because the methylation increases the bioaccumulation potential and limits the biodegradation of TCS. The concentrations of MTCS detected much higher, indicating that this might be due to the sediment foraging behavior of carp, which exposes them to higher levels of water-borne chemicals due to lipophilic nature. TCS and its metabolites have been detected in sediments, both freshwater and marine (Chalew and Halden, 2009).

Dioxins

The degradation and the transformation of TCS during manufacturing, incineration leads to dioxin toxicity in aquatic environment. The photolysis is the major pathway for

antimicrobial substance in the aquatic environment where the formation of 2, 8-dichlorodibenzodioxin (DCDD) and other dioxin derivatives were formed during the degradation of TCS in aqueous solutions. The conversion of TCS into dioxin by-products is dependent on both the pH and sunlight irradiation.

The photo degradation of TCS to dioxins in wastewater and reported that 2, 7/2, 8-dibenzodichloro-p-dioxin is a by-product of the TCS with 8 μg mL^{-1} of TCS were spiked in both water and wastewater samples. These results were consistent with phototransformation of triclosan and the degree of photolytic conversion is dependent upon the pH and the organic matter content of the sample. The photochemical reaction of triclosan accounts 80% loss of epilimnion region of Lake Greifensee during the season of summer. Aranami and Readman (2007) showed the intensity of TCS in freshwater and seawater samples with a low-intensity using artificial light source (irradiation) for a period of 12 days. The photodegradation of TCS to DCDD, occurred in 3rd day of irradiation in both freshwater and seawater samples with the concentration of 0.5–2.5% respectively. The majority of TCS is photolytically transformed into toxic by-products with the environmental factors (Aranami and Readman, 2007) resulting in high level of risk to both aquatic environments and humans.

Chlorophenols

The TCS also produce 2, 4-dichlorophenol and 2, 4, 6-trichlorophenol by photochemical process, which the US EPA (Environmental protection agency, United States) has pointed as priority pollutants and their formation by TCS. Greyshock and Vikesland (2006) reported that chlorophenols are the transformation products of TCS with the low levels of chlorine and chloramines. TCS reacted with free chlorine under drinking water conditions and 2, 4-dichlorophenol was formed through the ether cleavage of TCS, then undergoes electrophilic substitution to form 2, 4, 6-trichlorophenol.

Chloroform

Fiss *et al*. (2007) assessed the intensity of a dish soap containing TCS to form chloroform when added to chlorinated water and assessed after 5 min and 120 min, the concentration of chloroform was produced from 15 to 50 μg L^{-1} and the significant amounts of chloroform may be formed during the daily use of household products containing the antimicrobial properties. Fiss *et al*. (2007) indicated that, the amount of chloroform produced under certain conditions could be significant, which may place consumers at an increased risk for adverse health effects.

Effects of Triclosan on aquatic organisms

Triclosan is a ubiquitous because of continuous discharge of chemicals into waste water streams. The incomplete removal of triclosan results in contamination of water, soil and other organisms. Most of the drugs that targets humans, in which exhibits higher toxicity to many lower trophic organisms with the concentration of 0.07 to 0.15 mg L^{-1}, the significant changes in phytoplankton community that exposed to TCS with concentration as low as 15 ng L^{-1} and approximately 33% reduction in algal species richness at 150 ng L^{-1}.

The peak levels of Triclosan were recorded with the concentration of 3800 and 5160 ng L^{-1} in two sites of Tamiraparani River indicate the high risk on algal communities. Buser *et al*. (2006) reported the higher concentrations of Methyl-TCS were found in fish as high as 2100 ng g^{-1} (Veldhoen *et al*. 2006). Veldhoen *et al*. (2006) reported the effects of TCS on thyroxin- induced metamorphosis in frog tadpoles and some algae at a concentration ranged from 100 - 150 ng L^{-1}.The prematurity of tadpoles to frogs is because of the exposure to low levels (0.03 mg L^{-1}) of triclosan with disrupted thyroid hormone associated gene expression.

Effect of Triclosan in algae and invertebrates

Algae were determined to be the most susceptible organisms. It is the primary food source for many aquatic species, constitute a specific pathway for the accumulation of lipophilic water-borne contaminants, such as TCS (Capdevielle *et al.,* 2008). Due to continual exposure of TCS, leads to accumulation and degradation products in the tissues of aquatic organisms. From these measurements, bioaccumulation factor of TCS is about 1100 and 1600 μg kg^{-1} was estimated for parent compound and its methylated by-product. Coogan *et al*. (2007) reported that the TCS and MTCS concentration in filamentous algae (*Cladophora spp.*) in a receiving stream from the city of Denton (Texas) were ranged between 100–150 and 50–89 μg kg^{-1}, respectively. Bioaccumulation concentrations of TCS and MTCS in the tissues of snails were 500 and 1200 μg kg^{-1} and the algal bioaccumulation of TCS was 1400 and 1200μg kg^{-1}, respectively. The microalgae are very sensitive to triclosan (0.15 mg L^{-1}) than bacteria and fish. This finding provides evidence for the conversion of both TCS and MTCS in seawater, and their bioaccumulation potential. The MTCS is resistant to the processes of biodegradation and has the ability to persist in the environment for longer periods of time than the parent compound. Many aquatic invertebrates depend on algae as a source of nutrients, by which it leads to increase of TCS concentration in many aquatic organisms. About 5- 9054 nmol $L^{-1}$of TCS was measured in

algae and indicated that higher concentration of TCS may alter the community structure and affect the membrane metabolism of algae and cynobacteria in aquatic systems.

Fish

TCS and its byproducts have been detected in higher levels of concentration in fish from Tama River and Tokyo Bay, the samples of fish and shellfish were collected and analyzed for the TCS and MTCS concentration which was ranged between 1–38 μg kg^{-1} (whole body) and 3–20 μg kg^{-1} (shellfish samples). TCS concentration in samples of male bream (*Abramis brama*) living in Dutch surface waters, at relatively higher concentrations of 14 and 80 μg mL^{-1} which indicates that the accumulation of TCS takes place in the process of biomagnifications.

MTCS is a persistent pollutant with the potential to accumulate in the tissues of fish. The concentration of TCS in the plasma samples of 13 fish species from the detroited river, in the range of 750 to >10,000 pg g^{-1} of wet weight. Leiker *et al*. (2009) identified the MTCS concentration in male carp (*Cyprinus carpio*) with a mean concentration of 520–596 μg kg^{-1} per wet weight basis. In USA, Lozano *et al*. (2012) surveyed the presence of personal care products in fish samples from five effluent dominated rivers receiving discharge from WWTPs in large urban centers and rivers. The concentration of Triclosan in aquatic organisms and its acute toxicity was presented in the Table 1 and 2.

Table 1: Concentration of Triclosan (TCS) in aquatic organisms

Organisms	Type of Sample	TCS (μg kg^{-1})	References
Algae and invertebrates Filamentous algae (*Cladophora spp*.)	Whole organism	100–150	Coogan *et al.,* 2007
Freshwater snails (*Helisoma trivolvis*)	Muscle	50–300	Coogan and La Point, 2008
Atlantic bottle nose dolphins (*Tursiops truncates*)	Plasma	0.12–0.27	Fair *et al.,* 2009
Killer whale (*Orcinus orca*)	Plasma	9.0	Bennett *et al.,* 2009

Table 2: Acute toxicity of Triclosan on aquatic organisms

Compound: Triclosan

Category: Antimicrobial

Species	Trophic Ggroup	Duration	LC 50 (mg L^{-1})	References
Xenopus laevis	Amphibian	96 h	0.259	Batscher, 2006b
Acris blanchardii	Amphibian	96 h	0.367	Batscher, 2006b
Bufo woodhousii	Amphibian	96 h	0.152	Batscher, 2006b
Rana sphenocephala	Amphibian	96 h	0.562	Batscher, 2006b
Pseudokirch-neriella subcapitata	Algae	72h growth	0.53 (lg L^{-1})	Bazin *et al.,* 2010

Effect of Triclosan on microbial community

Svenningsen *et al*. (2011) observed that effects of triclosan on microbial communities and their degradation in simulated sewage-drain-field soil were decreased the microbial population about 22-fold in the presence of 4 mg kg^{-1} of triclosan. The broad range of TCS encompasses many types of Gram-positive and Gram-negative non-sporulating bacteria, fungi, *Plasmodium falciparum* and *Toxoplasma gondii*. It is bacteriostatic (it stops the growth of microorganisms) at low concentrations, but at higher concentrations they are bactericidal (it kills microorganisms).

The most sensitive organisms to triclosan are *Staphylococci, Streptococci, Mycobacteria*, *Escherichia coli* and *Proteus spp* at concentrations ranged from 0.01 mg L^{-1} to 0.1 mg L^{-1}. Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are also sensitive to triclosan in the range of 0.1–2 mg L^{-1}. The showering or bathing with 2% triclosan has been shown to be effective in decolonization of patients whose skin is carrying MRSA and also reported that *Enterococci* are much less susceptible than *Staphylococci* and *Pseudomonas aeruginosa* is highly resistant. The triclosan blocks the active site of enoyl acyl carrier protein reductase enzyme which is essential for fatty acid synthesis in bacteria and it affects the cell membrane and reproduction by preventing bacteria from fatty acid synthesis. Triclosan at lower concentration acts as a bacteriostatic and works against to type II fatty acid synthase enoyl reductase and at higher concentrations targets the cell membrane.

Triclosan toxicity in Animals

TCS interfering with the body's thyroid hormone metabolism led to hypothermic effect, lowering the body temperature, and overall causing a non- specific depressant effect on the central nervous system of mice. The triclosan exposure leads to decreased sperm production in male rats and also it blocks the metabolism of thyroid hormone, because it chemically mimics thyroid hormone, and binds to the hormone receptor sites, blocking them.

TCS enhances the production of chloroform in amounts up to 40% higher than levels in chlorine-treated tap water (Fiss *et al.,* 2007). Hao *et al*. (2007) reported that no formation of detectable chloroform levels over a range of expected tooth-brushing durations among subjects using toothpaste with triclosan and normal chlorinated tap water. US EPA classifies chloroform as a probable human carcinogen. As a result, triclosan was the target of a UK cancer alert, even though the amount of chloroform generated was less than normally present in treated chlorinated water and required brushing your teeth or washing your hands for times on the order of two hours or more.

Triclosan toxicity in Human health

Growing research has suggested that the impairment of reproductive health is associated with environmental exposure to many chemicals, such as EDCs (Xu *et al.,* 2022), which could influence reproductive health by regulating receptor binding, hormone biosynthesis, transport, metabolism, non-EATS pathways (Delbes *et al.,* 2022), and so on. TCS is an emerging endocrine disruptor that could give rise to reproductive disorders in both men and women (Raj *et al.,* 2021).

The other deleterious health effects mediated by TCS exposure in the past few years, such as the thyroid function damage), neurodevelopmental toxicity (Wang *et al.,* 2021), immune dysfunction (Zhao *et al.,* 2022), and cytotoxicity (Querido *et al.,* 2022). In cohort studies, TCS exposure was significantly correlated with the allergic disease in preschool children (Lin *et al.,* 2022), and the estrogenic effect of TCS might affect the prognosis of female breast cancer (Ilozumba *et al.,* 2022). Moreover, it was reported that TCS exposure triggered neurotoxicity (Wang *et al.,* 2022). Diao et al. (2022) recently elucidated that TCS exerted neurodevelopmental toxicity by upregulating miR-144 expression and causing abnormal regulation of neurologically related genes. Also, neurobehavioral toxicity was observed in the offspring of mice treated subcutaneously with TCS (Tran *et al.,* 2020). Zhang et al. (2018) investigated the potential effect of TCS exposure on the thyroid

function in SD rats and noted that TCS decreased thyroid hormone levels including total thyroxine (TT4), free thyroxine (FT4), total triiodothyronine (TT3), and free triiodothyronine (FT3) by restraining thyroid peroxidase (TPO).

Conclusion:

Triclosan is a synthetic antimicrobial agent with a long history. In recent years, TCS has been considered as a novel endocrine disruptor and long-term exposure to TCS could have unfavorable effects on human health. Several in vivo and in vitro studies have suggested a possible association between TCS exposure and multiple adverse health outcomes, such as the impairment of reproductive function, disturbance in hepatic lipid metabolism, kidney damage, colitis, and so on. However, there is a relative lack of mechanism-based human studies in terms of number and scope, and most cohorts and in vitro studies have predominantly evaluated the toxic effects induced by TCS exposure, without in-depth dissection of the specific mechanisms of action and cellular targets of TCS. Consequently, there is a great need for further work to focus on the underlying mechanisms of action of TCS exposure and characterize its toxic effects in animal and cell models.

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HERBAL COUGH MEDICINES: BRIDGING TRADITION AND SCIENCE

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Abstract:

The introduction highlights the prevalence of herbal-based cough medicines worldwide, with many preparations relying on herbal derivatives dissolved in various solvents, often with the addition of flavorings. These traditional remedies have been used for thousands of years, suggesting their potential benefits. However, there is no clear evidence linking the longevity of use to the pharmacologic effectiveness of these agents in treating cough. The introduction also either points out the limited scientific information available on the actions of most traditional cough medications, in laboratory models or controlled clinical trials. Additionally, the text touches upon the central and peripheral actions of antitussives in cough therapy, emphasizing the importance of addressing the underlying causes in many cases, such as excessive secretions or bronchospasm. It also highlights the use of herbal remedies for cough management, but acknowledges the lack of scientific validation for many of these popular herbal products. This chapter include the need for more research and scientific validation in the field of cough medicine, especially regarding the effectiveness of herbal remedies. It also acknowledges that despite the uncertainty surrounding their true therapeutic benefits, herbal medications will continue to be favoured by patients and healthcare providers due to their long history of use in managing this common symptom.

Keywords: Anti tussive, Cough, Herbal Remedies, Actions

Introduction:

Most popular cough medicines throughout the world are based on herbal derivatives dissolved in water, alcohol or other solvents, with the addition of flavorings such as honey, syrup or sugar. Most favoured preparations have been in use for treating coughs for thousands of years. The continuing acceptance of many of these agents would imply that those that are retained in use are of benefit, with the presumption that trial and error would have weeded out all but the most effective agents. However, this does not

appear to be the case, since there is no evidence that longevity of use correlates with pharmacologic effectiveness in alleviating cough. There is relatively little information on the actions of most traditional cough medications either in laboratory models or in controlled clinical trials, and current studies are more likely to be carried out on unconventional herbs, since any potential proprietary advantage could only be exploited if an unestablished herbal remedy was shown to be of value. The relevant chemical constituents in any potential plant phytomedicine are rarely recognized, and therefore the evaluation of any specific components is an uncommon occurrence in the clinical pharmacology of cough therapy.

Actions of cough medication

Medications are utilized in cough therapy not just to suppress cough but also to reduce the distress caused by repetitive coughing. Symptomatic relief may be required for chest pain or extra thoracic discomfort such as back pain, headache, fever and malaise. A productive cough may necessitate therapy either to correct the abnormality causing the production of sputum or to alter the quality of the secretions to make expectoration less difficult. A non-productive cough will need treatment to alleviate its etiologic pathology or to reduce its frequency. Many patients are particularly interested in the latter, and thus seek an antitussive to serve as a cough suppressor However; physicians should recognize that it is more important in most cases to relieve the etiology and to target therapy on the reversible airway abnormalities such as excessive secretions, abnormal sputum and bronchospasm. These issues may not require specific attention in the typical acute cough that accompanies viral infection, but they are of major significance in chronic coughs due to conditions such as asthma, post-nasal drip, gastro-oesophageal reflux, other causes of aspiration, bronchiectasis and cystic fibrosis.

Centrally acting antitussives

Agents that increase the medullary cough centre's threshold are the true antitussives that are well established in allopathic medicine. These drugs are derived from the poppy, Papiver somniferous; they include crude opium as well as its specific opioid components such as heroin, morphine, and codeine. The pharmaceutical industry has prepared many derivatives, but none is as effective as heroin. Since this highly potent antitussive is unacceptable as a medication, it has reverted to its herbal heritage as `folk remedy', although its popular illicit use cannot be ascribed to any recognition of its antitussive benefits by its devotees. The curious production of opiates by the poppy does

not appear to be mimicked by other plants, and the evolutionary value of such phytochemicals are not obvious, since only humans seem to be significantly affected by their psychic actions, and opiate addiction does not exist in other species. Placebos offer a major benefit in cough, and are presumed to act through the release of endorphins; thus they act as cerebral sedatives.

Peripherally acting antitussives

The most relevant action is that of bronchodilation, and the most renowned traditional antitussive bronchodilator herb is ma hunag, derived from the Chinese ephedra herb, Ephedra sinica [1]. This plant is the source of d-pseudoephedrine, l-ephedrine and other sympathomimetic agents. The prime effects of these phytochemicals is to relieve bronchospasm and mucosal congestion; thus ma huang and its constituents, ephedrine and pseudoephedrine, are acceptable therapies for pulmonary and nasal airway disorders. However, as is the case with heroin, these agents are now being abused as `folk medicines', since they are favored as stimulants, energizers, and anorexiants for weight loss. The Food and Drug Administration of the USA (the FDA) attempted to regulate the use of ma huang and ephedra alkaloids as `dietary supplements', but failed to introduce any legislative control. Although its general use in Western society is a tribute to both the overall combination of central and peripheral effects of ephedra alkaloids, ma huang remains an honoured drug in Traditional Chinese Medicine (TCM) for the therapy of respiratory tract disorders, including cough. Numerous other herbal remedies that are advocated as antitussives or cough therapies are presumed to act at a peripheral level, where they also affect mucociliary clearance [2, 3] However, both cocaine (from Erythroxylum coca) and marijuana (from Cannabis sativa), which have useful effects on lower airways, are favored as traditional `folk remedies' for their central effects, and they are popularly used for recreational purposes rather than as medications. Topical cocaine is an excellent anesthetic, and it is sometimes employed in bronchoscopy procedures to inhibit coughing. No other herbal product is so effective for this purpose, although the main product of Syzygium aromaticum, which is clove oil (eugenol), is known to be a weak topical anesthetic. Cloves are incorporated in the traditional Indonesian cigarette (kretek), but its possible value as a cough suppressant has not been evaluated. However, there have been concerns in the past that the use of clove cigarettes may induce the development of the adult respiratory distress syndrome (ARDS) in susceptible subjects. It is of interest that it was recently shown that clove oil enhances the surfactant effects of phospholipids;4

eucalyptus (or cineole, its main constituent) may havea similar effect.5 The smoke of marijuana can reduce bronchospasm in asthma,6 but continued use may lead to an increase in coughing since it can induce bronchitis. The effects of oral marijuana and its synthetic derivatives are not so dramatic in asthma; they have not been evaluated as specific therapy for cough, but the sedative and antiemetic effects of marijuana products suggests that suitable derivatives could reduce non-specific coughing.

Traditional herbal remedies for cough

Each country, each region, and each family utilize favored herbal antitussives. One of the most popular generally available remedies, Ricola1, contains a large number of traditional European herbs in several formulations: peppermint, coltsfoot, angelica, eucalyptus, horehound, mullein, hyssop, lemon balm, sage, thyme, linden, elder and lemon. The US Physician Desk Reference (PDR) for Herbal Medicines7 categorizes over 100 herbs as antitussives, although no acceptable laboratory or clinical studies have established the effectiveness of any of them. Coltsfoot was given the scientific name Tussilago farfara as a tribute to its historical acceptance as an antitussive [1]. Although it has been reported to contain a platelet activating factor (PAF) inhibitor,8 it has not been shown to be of benefit in cough therapy, and since it contains small amounts of hepatotoxic pyrrolizidine alkaloids, its use is not recommended. Similarly, one of the most popular herbal cough medicines in the USA, guaifenesin (derived from creosote), has not been shown to be an effective antitussive, and its mucolytic-expectorant effects have not been adequately demonstrated [2]. Many herbal cough medicines are used as lozenges and pastilles. These popular products rely on the presence of soothing demulcents such as mucilages, many of which are acidic polysaccharides derived from uronic acid. Macromolecular hydrocolloids, including sugars and gum arabic, absorb fluid; as they dissolve, they can produce a soothing covering in the throat, but they cannot give such protection to more distal sites of irritation or inflammation. Thus, they can reduce coughing only if the symptom is a reflex response to hyperactive or irritated receptors in the oropharynx. Mucilage-containing herbs such as mallow, Iceland moss, mullein, and plantain are favored by herbalists,[3] although their antitussive effects have not been adequately investigated. Saponins may have a surfactant effect, but these glycosidic molecules do not get absorbed in an active form from the bowel, and thus when taken orally they cannot exert a detergent effect on the mucous layer in the tracheobronchial tree.

Moreover, saponins are bitter and irritating when given topically, and are not suitable for inhalation. Thus, saponin-containing herbs such as ivy, primula, soap bark, grindelia and senega snake roots are unlikely to have a marked mucolytic effect, but their reflex stimulation of mucous secretion may result in an accompanying antitussive effect [4]. The essential oils of mint (menthol), eucalyptus (cineole), pine (pinene), myrtol (cineole, pinene and limonene), anise (anethole), thyme (thymol), turpentine (pinenes) and other popular herbal therapies can have an effect when given by mouth since they are absorbed into the blood stream and excreted by the lungs, where they may stimulate mucokinesis [5]. However, their value as antitussives, whether given by inhalation or gargles or taken by mouth, has not been adequately demonstrated. Their presence in cough medicines, teas, inhalants, rubs, and steam rooms is of unproven benefit with respect to a pharmacologic antitussive effect, although their extreme popularity suggests that they may have a physiologic action. Manufacturers and distributors of herbal antitussives often make claims that are unsubstantiated, and some provide pharmacologic explanations that lack any validity [6]. As an example, it is suggested by the manufacturer of one herbal remedy (that contains an extraordinary collection of herbal products) that skullcap is antispasmodic, lungwort relieves mucostasis, yerba santa is both a decongestant and an anti-inflammator, and so on [7]. Such explanations are used to justify their incorporations in multi-herb mixtures, but the effect of each component and of the total proprietary mixture is not supported by any scientific literature [8]. Nevertheless, some well-known products are enormously popular for treating coughs and colds; a prime example is Vicks Vaporub1, which contains menthol, camphor, turpentine spirits, eucalyptus oil, cedar leaf oil, myristica oil and thymol. Of these, only the use of menthol is supported by some laboratory and clinical evidence of effectiveness [9]. In the UK Friars' Balsam is a continuing favorite: it contains benzoin, storax, tolu balsam and aloes dissolved in alcohol. Another popular remedy is thymol, which is derived from thyme (Thymus vulgaris); it is widely advocated as an expectorant [10]. Thymol has antibacterial activity, but it is unlikely that this property is of relevance when it is used in conventional preparations for treating bronchitis [11-12]. Almost all these agents appear to be demulcents, but no mechanisms have been clearly attributed to most of them, and their effectiveness has not been assessed [13].

Antitussive herbs that are recommended in popular books available in English, and of the huge numbers of additional herbs that are described in other languages [14]. However, there is surprisingly little agreement between different authors, leading one to

conclude that most of these recommendations are totally lacking in validation and that the effectiveness of all these popular folk medicines as antitussives is dubious at best [15].

Conclusion:

Currently, the only herbal remedies known to be effective in treating coughs are the pungent spices (considered "hot" remedies) and menthol (a "cold" remedy). Other herbs may be considered somewhat promising, generating interest among researchers and experts in cough-related fields. Whether these herbs are merely placebos that provide comfort rather than proven scientific relief remains a question due to the substantial challenges and costs associated with conducting thorough studies. Nevertheless, the potential therapeutic properties of these herbs have spurred heated debates. In contemporary terms, herbal antitussive remedies have gained popularity among consumers, as they are often viewed as trendy food supplements that can be incorporated into a sophisticated diet. With confidence, one can recommend an herbal antitussive "menu" that includes chicken soup seasoned with pepper, garlic, ginger, and mint, followed by oysters enhanced with Tabasco sauce. This could be followed by a salad comprising onions, radish sprouts, and guava leaves. The main course, a simple glass of water, would precede a delectable, soothing, and mucilaginous dessert, all of which should be topped with mint tea infused with eucalyptus and liquorice. One can then select from a variety of herbs known to stimulate the brain's conversation centre while suppressing the cough reflex in the medulla. As long as it brings satisfaction, this meal should not have any adverse effects. However, it is important to note that conventional post-meal cigars should be avoided to prevent any coughing. At this point in our selection of antitussive options, it would be fitting to discuss the potential cough-relief qualities of one of the most important herbal agents: the fermented fruit of Vitis viniferous, prepared in accordance with traditional winemaking principles in various regions worldwide. Whether an antitussive is genuinely medicinal or functions as a placebo, a crucial requirement is that it pleases the person using it while adhering to the Hippocratic principle of doing no harm. Research in cough medicine will require more knowledge exchange and collegial debates to determine whether antitussives merely provide comfort without harm or offer measurable benefits that carry potential risks. Regardless of their role, herbal medications will continue to be favored by patients and their healthcare providers, as cough is one of the most common symptoms for which effective treatments are sought.

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HOW LIFE ORGANIZES ITSELF, MEMORY'S ROLE, AND HOW KNOWLEDGE GROWS

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Abstract:

The paper, employing a particular epistemological approach rooted in the extended version of complexity theory, delves into the boundaries between cognition and life. It explores the profound relationship between these domains, addressing themes such as memory as a distributed and multisystem natural phenomenon, the origin of meaning within the context of intricate self-organizing processes, and the intricate interplay among perception, learning (the assimilation of information), and thought (the active process of morphogenesis). Regarding the potential development of novel models concerning the knowledge-building process, the paper presents recent research findings that open up new frontiers. These discoveries are closely tied to a substantial conceptual shift in the analysis of the intricate interplay among information, meaningful complexity, memory, causality, teleology, and intentionality characterizing the natural facets of human cognition. In this context, the role of memory is depicted not merely as data storage in a static mental space but as a dynamic, profound process involving reconstruction and interconnection of internal self-reflective operations. This results in an evolutionary bricolage, a sequence of interconnected states, all integrated within a holistic framework through a dialectical synthesis encompassing form, function, and meaning.

Keywords: Memory, Self-Reflection, Human Cognition.

Introduction:

In the following article, we embark on a fascinating journey into the intricate workings of the human mind and its profound connection to the world we live in. Our guiding star on this voyage is the captivating framework of complexity theory, a lens through which we'll examine the intricate dance between cognition and life itself. At the heart of our exploration lies the concept of memory, which we'll view not as a mere

repository for facts and information but as a dynamic and multifaceted natural process. We'll uncover how memory isn't just about storing data but plays a vital role in helping us make sense of our experiences, thoughts, and the world around us.

Furthermore, we'll delve into the realms of learning and thinking, recognizing that these processes are not isolated but deeply intertwined. They form a cohesive web of understanding that shapes how we perceive and interact with our surroundings. It unveils the latest findings in research, shedding light on a revolutionary frontier. This frontier is intricately linked to a paradigm shift in how we analyze the intricate interplay between information, meaningful complexity, memory, causality, teleology, and intentionality – all of which are integral to the tapestry of human cognition. Within this context, memory isn't a static mental storage unit; rather, it emerges as a dynamic, ongoing process [1]. It involves the reconstruction of past experiences and the interconnection of internal self-reflective operations, allowing us to not just remember but to truly understand. The article draws parallels to the classical measure of Shannon information, which pertains to specific patterns of data in the simplest context. However, as we ascend to higher orders of complexity, we encounter intriguing dichotomies and multiple potentials existing simultaneously. This leads to what can be described as an evolutionary bricolage, a series of interconnected states, all harmoniously entwined within a holistic framework. This framework embodies a dialectical synthesis, seamlessly weaving together form, function, and meaning. In essence, our exploration hinges on a profound yet accessible idea: understanding is not merely about collecting isolated facts. It's about unravelling the intricate connections between these facts, constructing a richer tapestry of knowledge, and, in the process, gaining deeper insights into how we perceive and navigate the world.

Background

Exploring the relationship between cognition and life through the lens of complexity theory offers a unique and interdisciplinary perspective. This approach challenges conventional views of memory, learning, and thinking, making it relevant across fields like education, psychology, and artificial intelligence. It allows you to engage with cutting-edge research, encouraging critical thinking and personal growth. Ultimately, writing about this topic is an opportunity to contribute to a deeper understanding of human cognition and its complexities.

Complexity theory and biological information

In recent years, cognitive sciences, neurobiology, quantum mechanics, bio-mathematics, and bioinformatics on one hand, and functional semantics, non-standard semantics, and symbolic dynamics on the other hand, have progressively opened up new and fruitful research horizons, particularly in the field of complexity theory. This field represents an interdisciplinary study of adaptive complex systems, including natural and biological systems, and the associated emergent phenomena. The development of this theory, since the 1990s, has expanded beyond the examination of simple dissipative phenomena with a Markovian nature [2]. It now encompasses phenomena related to the coupled processing and transformation of information that occur in the subsequent formation of a biological information-processing system.

Thus, alongside the methodological reductionism of molecular biology in the study of cognitive activities, as exemplified by the work of Kandel and Squire, a holistic perspective has emerged [3]. This perspective doesn't trace its roots back to a vitalistic spirit but rather to mathematics itself. In this view, biological systems are no longer seen as equivalent to the sum of their parts, nor can they be solely determined by their initial conditions. Cognitive systems are complex, nonlinear (unpredictable), dissipative (exchanging energy with the environment), and capable of continually generating new information (order arises from chaos). In chaotic dynamics, it becomes possible to distinguish between energy flows and informational flows, which are mutually independent. Here, one can accurately recognize the specific interplay of complexity, self-organization, intentionality, and emergence that characterizes the natural forms of cognitive activity in every living system. In this context, the study of information transmission mechanisms, which underlie the processes of self-organization in the mind, is crucial.

In recent years, new mathematical models have been employed that can no longer be traced back to the tools offered by traditional Shannon's information theory, Boolean algebra, Halmos' theory, or Markov processes [4]. Unlike what has been advocated by figures such as Kandel, Squire, Damasio, and the Churchlands, information does not merely imply a message propagating on a medium, as in signal information theories or information management in general (computationalism) [5]. Instead, it signifies form + intentionality (embodied or biological information). This means actuality, the ability to inform through a form, imbuing matter not only with information but also actualizing the matter itself,

making it what it is already "disposed" to be. At this level, the intention is not to challenge the idea that consciousness is a natural process emerging from the brain, a viewpoint shared by Searle and Nagel, but rather to challenge the view that the brain constitutes a computational information-processing organ whose complexity depends solely on a vast number of biochemical interactions. This perspective represents an oversimplified concept of information compared to the sophistication of vital phenomena. This approach is predominantly derived from the realm of physics, mathematics, and computation, where the concept of complexity initially evokes limits of computability, unpredictability, and perhaps even "complication." Such an organized complexity concept, inherent in vital and cognitive phenomena, is not reducible to a mechanistic materialism on one hand, nor ascribable to a spiritual force on the other hand [6]. It is undoubtedly inspired by a "physicalist" vision. Nowadays, this perspective is being revisited thanks to new concepts such as incompleteness, incomputability, emergence, non-linearity, and semantic information. These concepts challenge ontological reductionism and biological determinism from within science. Moreover, they introduce the fundamental notion of meaningful complexity, intrinsically connected with not only extensional or syntactic information but also intentional information.

In light of these considerations, current research directions on cognitive functionalities, broadly speaking, have been moving away from the computational framework that originally generated them. Instead, they increasingly approach the interpretation of the mind as an emergent phenomenon linked to deep and distributed self-organization processes. This mind is no longer analyzable separately through standard models based on algorithmic procedures. It is viewed as an integrated entity, considering the dynamic unity of its parts that connect it to the brain-body, making it organismic [7]. Likewise, its synergistic and interactive relationship with the environment is considered organismic. As a result, the idea that a cognitive agent is something centralized and unified has been replaced by the concept of a disunified self. Modules, in fact, lack access to consciousness and introspection because they are not comprehensible to cognitive experience. Hence, the emergence of a cognitive self is not represented as a totality but rather as a series of emerging units within a disunified network. In light of all this, it can be asserted that the process of learning (the assimilation of information) now presents itself as morphogenesis (the emergence of form) rather than mere formatting. In other words, it

is an unpredictable process of increasing sophistication that can no longer be reduced to procedural or algorithmic simplification.

Memory as a natural and systemic process

In such a perspective, memory takes on the form of a distributed functionality, composed of different processing modes and inherent to various natural domains. Specific modulation systems play distinct roles within larger brain processing areas, such as the limbic system and the neocortex, which have been considered brain regions responsible for emotional and cognitive processes, respectively. These regions are dedicated to different levels of processing. However, even though these levels are distinguishable, they seem profoundly correlated and interconnected. It is within the areas of potential connection between the limbic system and the neocortex that neuroscientific research has located neural nuclei implicated in the processes of learning and memory. The definition of a multisystemic and distributed concept of memory, substantiated by advances in cognitive sciences and neurobiology, directs epistemological inquiry to consider, in a new light, the cognitive abilities of the subject and "the plurality of the factorial qualities of mnemonic processes [8]." This aims to clarify how "processing modes of memorization" tend to vary depending on the diversity of the provided learning stimuli. Memory, like knowledge, as a natural process, is deeply "stratified" and "situated" within lived memories, inside a cultural-symbolic system of shared intersubjective relationships. These relationships are essential for the construction, assimilation, and transmission of mnemonic products (epigenetic level), seen as "platforms of reference that are shareable and transferable." "The world (physical, natural, social) does not configure itself as an external, alien reality that dominates the subject, requiring adaptation to its laws. Nor is it, however, an amorphous scenario in which the subject engages as an expert manipulator of any possible reality, hypothesis, and forecast because everything is prefigurable and achievable in their mind. Instead, the world is the complex experiential dimension in which the developing subject constructs cognitive tools from time to time to adapt to situations and circumstances that call upon them and prompt them to open up, renew, and transform, while still preserving their internal organization and species identity." Despite some studies revealing a surprising degree of specialization within the cerebral cortex and confirming the notion that the storage of different types of memory relies on different brain regions in a category-specific manner, very little is known about the nature of the recall process for memories contained in explicit (declarative) memory [9]. This is a systemic

process that requires the involvement of the entire brain, thus involving the integration of the bottom-up approach (used in molecular biology) with the top-down approach (non-standard models) of cognitive sciences and complexity theory. In general, however, it can be inferred that memory is "an epigenetically marked process dependent on the maturation of the nervous system," deeply connected to the entirety of the cognitive system, from perceptual processes to higher mental processes, engaging various elements, from affectivity to motivational components, cognitive configuration modes to sophisticated and stratified thought-processing organizations."

Knowledge construction, and reality

Properties of extraordinary nature can emerge; indeed, one can argue that matter itself arises from complex energy exchange processes (force fields), processes already shaped by a form. The knowledge (understood as the "assimilation of information"), as well as memory, constitute highly complex processes that depend on particular dispositions of matter while not being reducible to it. At this level, the term "consciousness" is understood in the English sense of "consciousness," which indicates self-reflexivity. In Italian and in the human sciences, the term "coscienza" often refers to "moral consciousness [10]." In this sense, speaking of natural processes applied to memory and consciousness, conceived in the English sense, means identifying "natural processes" with "human processes," typical of the human species as part of nature. Regarding moral consciousness, according to this perspective, its preconditions are certainly natural and lie in intentionality, a fundamental characteristic of bios. In this sense, following the lines of research outlined in the field of bioeducational sciences and the epistemology of complexity, the concept of "form" can be described as a "dynamic process of growth," and what is of particular interest to psychogenetic investigation can manifest as the form of thought [11]. Thought is not merely a biological mechanism or genetic potentiality but, above all, intentionality that embodies itself in human symbolic language, creating ever-new meanings. Living beings are autopoietic systems, capable of producing their own identity by self-constructing constantly. Consequently, autopoietic systems, even if they undergo concrete changes, remain autonomous, in the sense that they subordinate every change to the maintenance of their own organization [12]. This progressive development of the concept of autonomy and organizational closure by biological sciences is an extremely interesting aspect of contemporary scientific paradigm that currently shifts reflections on form from the realm

of given structures (syntactic level of bios) to the world of unpredictable functional and systemic capacities of DNA (semantic level of bios).

In this regard, a behavior taking shape is always linked to a biological characteristic (synaptic plasticity), but it is only realized through contact with the environment and, in any case, is not determined by the "genetic program." In this sense, the optimal organization of a biological system, deeply related to the "meaningful-environment" surrounding it, should be considered an actual compromise between maximum variability on one hand and the highest degree of specificity on the other. The epistemological discourse can then refer to various modes of alignment with the variability of the ongoing informational principles. Invariance, indeed, which must be protected in a developmental situation, "relates to the unitary coordination of deep growth patterns. It is precisely within this dynamic relationship between surface and depth that we can find the telos aimed at making us understand how it is possible to maintain an identity of an analytical nature, even in the progressive and synthetic transformation of informational structures." In such a framework, the epigenetic structures that exist at the sensory level appear to be evolving filters, whose growth is indirectly guided by the intellect through successive changes in measurement patterns, probabilistic and relational, obtained through specific reflection procedures. In this sense, it can be hypothesized that this intricate path enables, at least in part, the indirect assimilation of external messages, assimilation that solidifies the coupling between the environment and internal self-organizing processes. Based on the findings obtained so far, it seems possible to assert that, at the level of complex cognitive systems, cognitive activity originates in the real, while simultaneously representing the necessary medium through which the real itself can come to establish itself objectively. In this sense, the objectivity of reality is also in line with the autonomy achieved by cognitive procedures. In such a framework, "reference procedures appear relative to the modes of actual constitution of effective alignment between vision and thought operations." They ensure the emergence not only of an adequate replica but of "cognitive autonomy in truth." Thus, emerges a method that is both a project, telos, and regulatory activity, a code that, becoming a process, also forms the basis for a continuously renewed synthesis between function and meaning. Reference procedures, therefore, play a guiding, analytical, and channeling role in relation to primary informational flows and the selective forces at play. They serve as the actual tools for the continuous renewal of the code, i.e., the emergence of ever-new incompressibility. Hence the possibility of defining new measures of complexity

and the real decline of continuous semantic reconstruction processes. It is only through a complete "reduction" at the first-order level (methodological reductionism) and a non-standard analysis at higher orders (holistic and teleonomic approach) that new incompressibility can effectively manifest at the practical level [13]. Thus, the concrete possibility of a connection between what is seen and what is not seen, between visual identification and thought regarding the connections between them, arises. Here emerges the alignment of the eyes of the mind with those of meaning, where meaning is understood as a "self-organizing form in action" that becomes "generativity and thought."

In light of all this, the observer's ability to constitute their measurements intrinsically becomes part of the same process of constituting data as data for the observer. Thus, at the epigenetic level, memory and meaningful complexity are closely connected to the unfolding, diachronically, of a holistic process characterizable only in terms of higher-order logic (morphogenesis in action). This process, within which the relationship of alternativeness between "world systems" manifests as the product of specific patterns in interference, is where the origin of teleonomic articulation that characterizes the process itself lies [14]. Memory function, therefore, takes the form of a dynamic and deep process of reconstruction and connection of internal self-reflection operations, rather than being a simple "storage" of data in a static mental space.

The Indian context

Exploring the topic of cognition, memory, and complexity theory within the Indian context holds immense significance. India's diverse educational landscape, characterized by a multitude of languages, cultures, and educational systems, presents a unique opportunity to delve into the intricacies of how cognition operates in such diversity. This exploration can yield invaluable insights for educators and policymakers seeking to tailor teaching methods to the diverse needs of Indian students. Moreover, India's educational challenges, including overcrowded classrooms and resource disparities, call for context-specific solutions, and understanding memory and learning complexities can contribute to more effective educational strategies. Culture plays a pivotal role in cognitive processes, making it essential to investigate how Indian culture and traditions influence memory, learning, and thinking [15]. This cultural perspective is vital for crafting education and communication approaches that resonate with the values and beliefs of Indian individuals. Additionally, with India's rapid technological advancements, particularly in IT and digital

sectors, a study of how cognition adapts to the digital age is crucial. This is particularly relevant given the increasing prevalence of online education and digital learning platforms. Lastly, socioeconomic factors in India significantly impact cognitive development and learning outcomes. Analyzing the interplay between these factors and cognitive processes can contribute to addressing issues of educational equity and social justice. An in-depth exploration of cognition and memory, grounded in complexity theory, within the Indian context can inform more effective education, foster cultural sensitivity, adapt to the digital era, and promote social equality, ultimately leading to enhanced learning experiences and societal progress.

Conclusion:

The intricate relationship between knowledge, memory, consciousness, and the natural world within the context of contemporary scientific paradigms and epistemological perspectives. It emphasizes that knowledge and memory are highly complex processes deeply intertwined with the material world, although they cannot be solely reduced to it. Instead, they are part of the ongoing interplay between human cognition and the external environment. The discussion delves into the concept of consciousness, drawing a distinction between the English sense of "consciousness" as self-reflexivity and the Italian or moral sense of the term. It highlights the importance of intentionality in understanding consciousness and how it is embodied in human symbolic language, leading to the creation of new meanings. It also touches upon the notion of autonomy in biological systems, particularly in the context of cognitive processes. It emphasizes that living beings are autopoietic systems, constantly self-constructing their identity. Autonomy is seen as a key aspect of this self-organization, allowing for adaptation to the environment while maintaining internal organization. It underscores the importance of understanding the connection between what is seen and what is not seen, as well as the role of reference procedures in bridging this gap. It contemplates the complex and dynamic nature of knowledge, memory, and consciousness within the broader framework of natural processes, emphasizing their interdependence with the external world and their role in shaping our understanding of reality.

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NANOCARRIERS FOR TOPICAL DELIVERY

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Abstract:

Topical drug delivery is a widely employed method for the treatment of various dermatological and transdermal conditions, offering localized and systemic therapeutic benefits. However, challenges such as limited drug permeation, poor stability, and patient compliance have prompted the development of innovative strategies to enhance the efficacy of topical formulations. Nanocarriers, including nanoparticles, liposomes, and nanoemulsions, have emerged as promising solutions to address these issues. This abstract provides an overview of the utilization of nanocarriers in topical delivery systems. Nanocarriers offer unique advantages, such as improved drug solubility, controlled release, and the ability to encapsulate a wide range of therapeutic agents, from small molecules to biologics. Moreover, their small size and surface properties can enhance drug penetration and target specific skin layers or pathological sites, thereby optimizing therapeutic outcomes. The discussion covers various nanocarrier types, their preparation methods, and their influence on drug stability and release kinetics. Furthermore, it explores recent advancements in nanocarrier design, including surface modifications for prolonged retention and triggered release mechanisms, which contribute to enhanced drug delivery precision and patient comfort. In conclusion, nanocarriers for topical delivery represent a burgeoning field with great potential to revolutionize the treatment of skin-related disorders. The continued development of nanotechnology-based delivery systems offers the promise of more effective, convenient, and patient-friendly solutions for a wide range of dermatological and transdermal applications.

Keywords: Nanocarriers, Permeation enhancement, Percutaneous absorption, Bioavailability

Introduction:

The field of nanotechnology has made significant strides in various scientific and medical applications, including drug delivery systems. Nanocarriers, with their unique properties and versatile applications, have gained considerable attention in the realm of topical drug delivery. This chapter explores the use of nanocarriers for topical delivery, highlighting their benefits and potential in enhancing the efficacy of therapeutic agents.

Topical drug delivery

Topical drug delivery refers to the administration of medications or therapeutic agents directly onto the skin or mucous membranes for local or systemic effects. This method of drug administration is commonly used for various medical purposes, including treating skin conditions, managing pain, and delivering medications to specific areas of the body. Here's an overview of topical drug delivery:

Types of topical drug delivery

Dermal: This involves applying medications to the skin's surface for local or systemic effects. Dermal drug delivery includes creams, ointments, gels, patches, and transdermal delivery systems [1,2].

Mucosal: Drugs can be applied to mucous membranes such as the eyes, nose, mouth, and rectum. This route is used for treating conditions like eye infections or providing local anesthesia [3,4].

Advantages of topical drug delivery

Localized action: Topical delivery allows medications to target specific areas without affecting the entire body, minimizing systemic side effects.

Ease of administration: It's a non-invasive and convenient method, often preferred by patients.

Reduced first-pass metabolism: For transdermal delivery, drugs bypass the liver, reducing first-pass metabolism and enhancing bioavailability.

Prolonged release: Transdermal patches can provide controlled, prolonged drug release [5].

Factors influencing drug permeation

Skin thickness: Thinner skin areas typically absorb drugs more readily.

Drug properties: Lipophilic drugs tend to penetrate the skin better.

Formulation: The choice of vehicle (cream, gel, ointment) affects drug release and absorption.

Skin condition: Damaged or inflamed skin may alter drug absorption [6-8].

Importance of targeted topical delivery

Targeted topical delivery refers to the precise and localized administration of drugs, therapeutic agents, or other substances to a specific area of the skin or mucous membranes. This approach has several important advantages and applications, making it a valuable strategy in various fields, including medicine, dermatology, and cosmetics.

Targeted topical delivery offers numerous advantages, including increased treatment efficacy, reduced systemic exposure, improved patient compliance, and decreased side effects. Its applications extend across various medical, dermatological, and cosmetic fields, making it an important strategy in healthcare and therapeutic development.

Nanocarriers

Nanotechnology has the potential to revolutionize medicine in various ways by providing new tools and techniques for diagnosing and treating diseases.

Nanotechnology holds great promise in medicine, it also poses challenges, including safety concerns related to potential toxicity, the need for regulatory oversight, and the development of scalable and cost-effective manufacturing methods. Researchers and regulators are working to address these issues to harness the full potential of nanotechnology in improving healthcare and medical treatments.

Types of nanocarriers

- Liposomes: Liposomes are a type of lipid-based nanoparticle that has gained significant attention in the field of drug delivery, including topical drug delivery. They can be used to encapsulate various drugs, vitamins, and other bioactive compounds for targeted and controlled release on the skin or mucous membranes. Liposomes offer several advantages for topical delivery, including enhanced skin penetration, improved stability of the encapsulated compounds, and reduced side effects. Here are some key points about liposomes for topical delivery [9]:
    - Enhanced Skin Penetration
    - Encapsulation of Hydrophilic and Lipophilic Compounds
    - Controlled Release
    - Reduced Irritation
    - Improved Stability
    - Targeted Delivery

- Flexibility in Formulation
- Cosmetic and Dermatological Applications

Despite their advantages, liposomal formulations may face challenges such as limited stability over time, difficulty in maintaining drug encapsulation efficiency, and potential issues related to scale-up production.

Overall, liposomes are a promising technology for topical drug delivery, and their potential applications extend to various fields, including pharmaceuticals, cosmetics, and dermatology. Researchers continue to explore and optimize liposomal formulations to improve their efficacy and safety for topical use.

- Nanoparticles: Nanoparticles have gained significant attention in the field of drug delivery, including topical delivery, due to their potential to improve the efficacy and targeted delivery of therapeutic agents. Topical delivery refers to the application of drugs or other active substances to the skin, mucous membranes, or other external body surfaces. Nanoparticles can be used to encapsulate and deliver various types of drugs, including pharmaceuticals, cosmetics, and other bioactive compounds [10]. Here are some key points about the use of nanoparticles for topical delivery:

Types of nanoparticles

- Lipid-based nanoparticles: Lipid nanoparticles, such as liposomes and solid lipid nanoparticles (SLNs), are commonly used for topical drug delivery. They consist of lipids or lipophilic materials and can encapsulate both hydrophilic and hydrophobic drugs.
- Polymeric nanoparticles: Polymeric nanoparticles are made from biodegradable polymers, such as poly(lactic-co-glycolic acid) (PLGA) and chitosan. They are versatile carriers for a wide range of drugs and have sustained release capabilities.
- Inorganic nanoparticles: Inorganic nanoparticles like gold nanoparticles and silver nanoparticles have been explored for their potential in topical drug delivery, as they offer unique properties and drug release mechanisms.

Advantages of nanoparticles for topical delivery

- Enhanced penetration: Nanoparticles can improve the penetration of drugs into the skin, allowing for better absorption and therapeutic effects.
- Controlled release: Nanoparticles enable controlled and sustained release of drugs, which can maintain therapeutic levels over an extended period.

- Targeted delivery: Functionalization of nanoparticles can enhance targeted delivery, allowing drugs to be directed to specific skin layers or cells.
- Protection of active ingredients: Nanoparticles can protect sensitive or easily degraded active ingredients from external factors like light and air.
- Improved Stability: Nanoparticles can enhance the stability of drugs and prevent their degradation.

Nanoparticles offer promising opportunities for topical drug delivery, enhancing the effectiveness of treatments for skin diseases and cosmetic products. However, it is essential to consider safety and regulatory aspects when developing and using nanoparticle-based topical formulations.

- Nanoemulsions: Nanoemulsions are a type of emulsion with very small droplet sizes, typically in the nanometer range. They are commonly used in various industries, including pharmaceuticals and cosmetics, for the delivery of active ingredients. When it comes to topical delivery, nanoemulsions offer several advantages such as enhanced skin penetration, improved stability, cosmetically elegant, controlled release, compatibility with various active ingredients, reduced irritation and ease in manufacturing.

Nanoemulsions can be used for various topical applications, including skincare products, sunscreens, anti-aging creams, and pharmaceutical preparations. They have gained popularity in the industry due to their ability to improve the effectiveness and sensory characteristics of topical products. However, it's important to consider factors such as formulation stability, safety, and regulatory requirements when developing and using nanoemulsions for topical delivery.

- Dendrimers: Dendrimers are highly branched, three-dimensional macromolecules that have been studied for various applications, including drug delivery. They offer several advantages for topical drug delivery such as adhesion and bioadhesion, enhanced drug solubility, drug encapsulation, minimized systemic absorption and improved stability.

It is important to note that the design, size, and surface properties of dendrimers need to be carefully tailored for specific drug delivery applications. Additionally, safety and biocompatibility are crucial considerations when using dendrimers in topical formulations, as they come into direct contact with the skin or mucous membranes. Research in this field

is ongoing, and scientists are continually exploring new ways to harness the potential of dendrimers for effective and safe topical drug delivery.

- Nanofibers: Nanofibers are ultra-thin fibers with diameters in the nanometer range (typically less than 100 nanometers). They have gained significant attention in the field of drug delivery, including topical delivery, due to their unique properties and potential advantages.

While nanofiber-based drug delivery systems offer numerous advantages, there are still challenges in scaling up production, ensuring product stability, and achieving regulatory approval for these innovative delivery methods. Nonetheless, ongoing research and development in this field continue to expand the possibilities of using nanofibers for topical drug delivery.

- Solid lipid nanoparticles: Solid lipid nanoparticles (SLNs) are a type of nanoparticle system that has gained significant attention in the field of pharmaceutical and cosmetic science for their potential as carriers for topical drug and cosmetic ingredient delivery. SLNs are submicron-sized particles composed of lipids that are typically in a solid state at room temperature. They offer several advantages for topical delivery applications.

When formulating SLNs for topical delivery, factors such as lipid selection, particle size, surface charge, and payload compatibility must be carefully considered to optimize their performance. Additionally, stability and quality control of SLN formulations are crucial to ensure the long-term effectiveness of the product.

It's worth noting that while SLNs offer many advantages, they may also have limitations, such as the potential for particle aggregation or drug expulsion. Researchers continue to explore ways to address these challenges and improve the performance of SLNs for topical applications.

Benefits of nanocarriers for topical delivery

Nanocarriers offer several advantages for topical drug delivery and cosmetic applications, thanks to their unique properties and potential to improve the therapeutic or cosmetic effects of products. Some of the benefits of using nanocarriers for topical delivery include [11,12]:

- Enhanced skin penetration: Nanocarriers, such as lipid nanoparticles (liposomes, solid lipid nanoparticles, and nanostructured lipid carriers) and polymeric

nanoparticles, can encapsulate and deliver drugs or active ingredients deep into the skin layers, allowing for improved bioavailability and therapeutic efficacy.

- Controlled release: Nanocarriers can be designed to release the encapsulated substances gradually over time. This controlled release can lead to a sustained therapeutic effect, reducing the need for frequent reapplication and improving patient compliance.
- Protection of active ingredients: Nanocarriers protect sensitive or easily degraded substances from environmental factors like light, heat, and oxygen, ensuring the stability and efficacy of the encapsulated compounds.
- Targeted delivery: Functionalization of nanocarriers with ligands or surface modifications can enable targeted delivery to specific skin layers, cells, or tissues, increasing the precision of treatment and minimizing potential side effects.
- Reduced side effects: By delivering drugs or active ingredients directly to the affected area, nanocarriers can reduce systemic absorption and minimize the risk of systemic side effects, which is especially important for potent medications.
- Improved cosmetic effects: Nanocarriers can enhance the appearance and texture of the skin by delivering ingredients like antioxidants, peptides, or vitamins, promoting hydration, and reducing the signs of aging.
- Reduced use of excipients: Nanocarriers can decrease the need for additional excipients, such as emulsifiers or stabilizers, in topical formulations, simplifying the product's composition and potentially reducing the risk of skin irritation.
- Better patient compliance: Topical products with nanocarriers often have a pleasant texture and improved skin feel, making them more appealing to consumers and encouraging consistent use.
- Versatility: Nanocarriers can encapsulate a wide range of substances, including hydrophobic and hydrophilic drugs, making them suitable for a variety of therapeutic and cosmetic applications.
- Potential for combination therapy: Nanocarriers can be used to deliver multiple active ingredients simultaneously, allowing for combination therapy to address different aspects of a skin condition or cosmetic goal.
- Tailored physicochemical properties: Nanocarriers can be designed with specific particle size, charge, and surface properties to optimize their interaction with the skin and enhance the desired therapeutic or cosmetic effects.

Despite these benefits, it's essential to note that the development and use of nanocarriers in topical applications require rigorous safety and efficacy assessments, as well as consideration of regulatory guidelines to ensure the products meet quality and safety standards.

Factors influencing the design of nanocarriers

The design of nanocarriers, which are nano-sized delivery systems for drugs, genes, and other therapeutic agents, is influenced by a variety of factors to ensure their effectiveness and safety. These factors can vary depending on the specific application and the characteristics of the payload being delivered. Here are some key factors that influence the design of nanocarriers [13-17]:

Drug or payload properties:

- Solubility: The solubility of the drug or payload in the nanocarrier matrix can affect the design. Hydrophobic drugs may require different carrier materials than hydrophilic ones.
- Molecular weight: The size and molecular weight of the drug can impact the choice of nanocarrier and the loading capacity.

Targeted delivery:

- Target tissue or organ: The intended site of action influences the choice of nanocarrier size, surface functionalization, and release mechanisms.
- Active targeting: Designing nanocarriers with ligands or antibodies for specific receptors on target cells can enhance drug delivery to desired locations.

Release kinetics:

- Controlled release: The desired release profile, such as sustained or triggered release, will influence the choice of nanocarrier design and materials.
- Burst release: Some applications may require an initial burst release of the payload, followed by sustained release.

Size and shape:

- Particle size: The size of nanocarriers affects their circulation time, biodistribution, and cellular uptake. Smaller nanoparticles often have better tissue penetration.
- Shape: Nanocarrier shape can influence cellular uptake, circulation, and interactions with biological systems.

Surface modification:

- Surface charge: The surface charge of nanocarriers can influence their stability, cellular uptake, and interactions with plasma proteins.
- Surface functionalization: Adding targeting ligands, polymers, or other molecules to the nanocarrier surface can improve specificity and drug release.

Biocompatibility and toxicity:

- Materials: The choice of nanocarrier materials must consider their biocompatibility and potential toxicity.
- Degradation: The rate of nanocarrier degradation and clearance from the body is crucial to minimize toxicity and ensure safety.

Stability:

- Physical stability: Nanocarriers should maintain their integrity during storage and in biological environments.
- Chemical stability: The payload and nanocarrier should not undergo chemical reactions that affect their functionality.

- Manufacturing scalability: The chosen manufacturing method should be scalable to produce nanocarriers in sufficient quantities for clinical use.
- Regulatory requirements: Nanocarrier design should adhere to regulatory requirements for safety and efficacy, which can vary by region.
- Cost and economics: The cost of manufacturing the nanocarriers can be a significant factor, especially for widespread clinical applications.
- Environmental impact: The environmental impact of nanocarrier production and disposal should be considered.
- Patient compliance: The mode of administration and patient comfort may influence nanocarrier design.

Designing effective nanocarriers requires a careful balance of these factors, and often a multidisciplinary approach involving materials science, pharmaceutical sciences, and biomedical engineering to meet the specific needs of the intended application.

Applications of nanocarriers in topical delivery

Nanocarriers, such as nanoparticles and liposomes, have gained significant attention in the field of topical drug delivery due to their ability to enhance the therapeutic efficacy of drugs while minimizing side effects. Here are some key applications of nanocarriers in topical delivery [18-22]:

- Skin diseases: Nanocarriers can be used to deliver drugs for the treatment of various skin diseases, including psoriasis, eczema, and acne. They help in improving the penetration of drugs into the skin and target the affected areas more effectively.
- Sunscreen and cosmetic products: Nanocarriers can enhance the stability and effectiveness of sunscreens and cosmetic products. They can encapsulate UV filters and other active ingredients, ensuring better skin protection and prolonged release of active agents.
- Anti-aging products: Liposomes and nanoparticles can encapsulate anti-aging compounds like retinoids and peptides, allowing them to penetrate the skin more efficiently and deliver their benefits, such as wrinkle reduction and skin rejuvenation.
- Wound healing: Nanocarriers can be used to deliver growth factors, antimicrobial agents, and other wound-healing substances to accelerate the healing process. They can protect the wound from infection and facilitate tissue repair.
- Topical anesthetics: Nanocarriers can improve the delivery of local anesthetics, making them more effective and reducing the pain associated with medical procedures or conditions.
- Transdermal drug delivery: While not strictly topical, transdermal delivery systems, such as patches and creams, can benefit from nanocarriers to increase drug permeation through the skin, allowing for prolonged and controlled release of medications.
- Acne treatment: Nanocarriers can encapsulate antibacterial agents, retinoids, or anti-inflammatory drugs for the treatment of acne. They help in targeting the sebaceous glands and reduce the side effects associated with these treatments.
- Topical antifungals: Nanocarriers can improve the delivery of antifungal drugs for conditions like fungal infections of the skin, nails, or mucous membranes.
- Topical antibiotics: They can be used to deliver antibiotics for the treatment of localized skin infections or as a prophylactic measure during surgeries or invasive procedures.
- Enhanced permeation: Nanocarriers can improve the permeation of active ingredients across the skin barrier by exploiting the principles of nano-sized particles, lipophilic/hydrophilic properties, and surface modifications.

- Targeted drug delivery: Nanocarriers can be functionalized with ligands or antibodies to target specific cells or receptors in the skin, which is particularly useful for treating skin cancers and other conditions.
- Treatment of hyperpigmentation: Liposomes and nanoparticles can deliver agents for the treatment of hyperpigmentation disorders, such as melasma or age spots.
- Localized therapy: They can help in providing localized therapy for conditions like atopic dermatitis, by delivering drugs directly to the affected areas, reducing systemic exposure.

Nanocarriers have the potential to revolutionize the field of topical drug delivery by improving drug stability, enhancing penetration, and allowing for controlled release. However, it's essential to conduct rigorous safety and efficacy studies to ensure their practical application in various dermatological and cosmetic formulations.

Safety and toxicity concerns

Nanocarriers, such as nanoparticles and liposomes, are increasingly being explored for topical drug delivery due to their potential to enhance the therapeutic efficacy of drugs and reduce side effects. However, there are safety and toxicity concerns associated with the use of nanocarriers in topical delivery. Here are some of the key considerations:

- Skin irritation and sensitization: Nanocarriers can potentially irritate or sensitize the skin. The size, surface charge, and composition of nanoparticles can influence their interaction with the skin. Some nanoparticles may cause skin irritation or allergic reactions, especially when they penetrate the stratum corneum and come into contact with underlying skin layers.
- Skin permeation and penetration: The ability of nanocarriers to penetrate the skin barrier can be advantageous for drug delivery but can also raise concerns. Deep penetration into the skin may lead to the systemic absorption of the drug, potentially causing unintended side effects or systemic toxicity.
- Skin barrier disruption: Certain nanocarriers, if not properly designed, can disrupt the skin barrier, compromising its integrity and allowing for increased penetration of harmful substances, including pathogens. This can lead to infections or other skin disorders.
- Toxicity of nanomaterials: The toxicity of the nanomaterials themselves is a critical concern. Some nanoparticles, like silver or certain metal oxide nanoparticles, can be

toxic to skin cells. The release of metal ions from these nanoparticles can lead to oxidative stress and inflammation.

- Allergenicity: Some nanomaterials may trigger allergic responses in individuals with preexisting sensitivities. It's important to evaluate the allergenic potential of nanocarriers before their use in topical formulations.
- Nanoparticle accumulation: Prolonged use of topical products containing nanocarriers can potentially lead to the accumulation of nanoparticles in the skin or other tissues. The long-term consequences of this accumulation are not fully understood and warrant further investigation.
- Regulatory compliance: Regulatory agencies like the FDA (U.S. Food and Drug Administration) have specific guidelines and requirements for the safety assessment of nanocarriers used in topical products. Manufacturers need to ensure compliance with these regulations.

To address these safety and toxicity concerns, it is crucial to conduct thorough preclinical and clinical studies to assess the safety profile of nanocarriers. These studies should include skin irritation and sensitization testing, skin permeation studies, and toxicity assessments. Additionally, the design and engineering of nanocarriers should aim to minimize skin barrier disruption and toxicity, while maximizing drug delivery efficiency. Overall, while nanocarriers offer significant potential for improving topical drug delivery, their safety and toxicity concerns must be rigorously evaluated and managed to ensure their safe and effective use in topical formulations.

Regulatory considerations

The use of nanocarriers in topical drug delivery has gained significant attention in recent years due to their potential to improve the efficacy and safety of various pharmaceutical and cosmetic products. However, the development and commercialization of nanocarriers for topical delivery are subject to various regulatory considerations to ensure their safety and efficacy. Here are some key regulatory considerations for nanocarriers in topical delivery:

Regulatory agencies

Different countries have their regulatory agencies responsible for overseeing the approval and safety of pharmaceuticals and cosmetic products. In the United States, the Food and Drug Administration (FDA) regulates pharmaceuticals, while the Cosmetic Ingredient Review (CIR) evaluates the safety of cosmetic ingredients. In the European

Union, the European Medicines Agency (EMA) and the European Commission regulate pharmaceuticals, and the European Cosmetic Regulation 1223/2009 governs cosmetics. Companies must adhere to the guidelines and regulations set forth by these agencies.

Safety and toxicology assessment:

Nanocarriers used in topical delivery must undergo comprehensive safety and toxicology assessments. This includes evaluating the potential for skin irritation, sensitization, cytotoxicity, and any systemic toxicity. Preclinical studies may be required to assess these parameters.

Quality and manufacturing:

Regulatory agencies often require manufacturers to adhere to good manufacturing practices (GMP) to ensure product quality, consistency, and purity. Detailed information about the nanocarrier's composition, manufacturing processes, and quality control methods should be submitted to regulatory authorities.

Labeling and claims:

Proper labeling of products is crucial. Manufacturers must accurately describe the nanocarrier-based topical product's ingredients and their concentration. Any therapeutic or cosmetic claims must be supported by scientific evidence, and the product label should not be misleading.

Product classification:

Regulatory requirements can vary based on whether the product is classified as a pharmaceutical or cosmetic. In many cases, the intended use and claims made for the product can determine its classification and the regulatory pathway it must follow.

Biocompatibility and biodegradability:

Nanocarriers should be designed to be biocompatible and biodegradable. Regulatory agencies may require data on the biocompatibility of the nanomaterials and the rate of degradation to ensure that they do not pose long-term risks to the skin or the environment.

Stability and shelf life:

Stability studies are important to establish the product's shelf life. Data should be provided to demonstrate that the nanocarriers remain stable and maintain their integrity during storage and use.

Documentation and regulatory submissions:

Manufacturers must compile comprehensive documentation, including data from safety and efficacy studies, as well as information on manufacturing processes, quality control, and product specifications. These documents are submitted to regulatory agencies as part of the approval process.

Post-market surveillance:

After product approval and market launch, post-market surveillance is essential to monitor any adverse events or unexpected side effects associated with the use of nanocarrier-based topical products. This information may lead to product recalls or labeling changes.

It's important for manufacturers of nanocarrier-based topical products to work closely with regulatory authorities and seek their guidance throughout the product development and approval process. The regulatory landscape may evolve, so staying informed about the latest guidelines and requirements is crucial for ensuring compliance and bringing safe and effective products to the market.

Future trends

Nanocarriers have shown significant potential in the field of topical drug delivery, and several future trends and developments are expected in this area. These trends are driven by the need for more effective and targeted delivery of drugs and therapeutic agents to the skin, as well as the desire to overcome various challenges associated with topical drug administration.

The future trends in nanocarriers for topical delivery represent an exciting frontier in drug delivery and skincare. The continued development of these technologies holds the promise of more effective and patient-friendly treatments for a wide range of dermatological conditions and cosmetic applications.

Conclusion:

Nanocarriers for topical delivery represent a promising avenue for improving the therapeutic outcomes of various skin conditions and for enhancing the delivery of cosmetic and dermatological products. With continued research and development, nanotechnology is expected to play an increasingly pivotal role in revolutionizing the field of topical drug delivery, offering more effective and targeted treatments with reduced side effects. However, researchers must also address safety and regulatory concerns to bring these innovations to the market, ultimately benefiting patients and consumers alike.

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THE ENVIRONMENTAL IMPACT OF PHARMACEUTICAL WASTE: RISKS AND CONSEQUENCES

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Abstract:

Pharmaceutical waste management is a critical facet of healthcare and environmental sustainability. This paper explores the diverse dimensions of pharmaceutical waste management, emphasizing the need for safe and responsible disposal of pharmaceutical products. It delves into the wide-ranging environmental impacts of pharmaceutical waste and the risks it poses to public health. The management of pharmaceutical waste necessitates a combination of regulatory guidelines, best practices, and advanced technologies for the safe handling and disposal of these materials. This dynamic field is continually evolving as new pharmaceuticals and healthcare products emerge, and regulations adapt to address emerging challenges. Recognizing the environmental and health implications of pharmaceutical waste, effective management strategies become increasingly vital to minimize risks and promote sustainability.

Keywords: Antibiotic resistance, Aquatic toxicity, Incineration, Landfilling, Wastewater treatment

Introduction:

Pharmaceutical waste management is a critical aspect of healthcare and environmental stewardship that involves the safe and responsible disposal of pharmaceutical products, including expired medications, unused drugs, and various healthcare-related materials. Proper pharmaceutical waste management is essential to protect public health, prevent environmental contamination, and ensure regulatory compliance. Pharmaceutical waste can take various forms, such as expired or unused prescription and over-the-counter drugs, pharmaceutical packaging, contaminated materials, and even biologically hazardous substances like needles and syringes. Inappropriate disposal of these substances can lead to several adverse consequences,

including the risk of medication misuse, environmental pollution, and the spread of infectious diseases [1].

The management of pharmaceutical waste typically involves a combination of regulatory guidelines, best practices, and advanced technologies to ensure the safe collection, transportation, and disposal of these materials. Healthcare facilities, pharmacies, and individuals all have important roles to play in adhering to proper disposal procedures. This field of waste management is continuously evolving as new pharmaceuticals and healthcare products are developed, and regulations adapt to address emerging challenges [2,3]. As societies become more aware of the environmental and health implications of pharmaceutical waste, effective management strategies become increasingly essential to minimize the associated risks and promote sustainability.

Pharmaceutical waste:Types and sources

Pharmaceutical waste refers to any materials associated with the production, administration, or use of pharmaceutical products that are no longer needed or have become unusable. It is a diverse category of waste that poses unique challenges due to the potential environmental and health risks associated with improper disposal. Pharmaceutical waste can be categorized into several types, and its sources primarily originate in healthcare settings and households.

Types of pharmaceutical waste [4]

- Solid pharmaceutical waste: This includes expired or unused medications, empty pill bottles, blister packs, and liquid medicine containers, as well as contaminated items such as gloves, masks, and bandages.
- Liquid pharmaceutical waste: This includes wastewater from pharmaceutical manufacturing plants, hospital pharmacies, and other healthcare facilities. Liquid pharmaceutical waste can contain a variety of pharmaceuticals, as well as solvents, cleaning agents, and other chemical residues.

Sources of pharmaceutical waste

- Healthcare facilities: Hospitals, clinics, and other healthcare facilities generate a significant amount of pharmaceutical waste, including expired or unused medications, contaminated medical supplies, and wastewater from hospital pharmacies [5].

- Pharmaceutical manufacturing plants: Pharmaceutical manufacturing plants generate pharmaceutical waste in the form of unused raw materials, expired or defective products, and wastewater from manufacturing processes.
- Research laboratories: Research laboratories generate pharmaceutical waste in the form of unused or expired research chemicals and biological materials.
- Households: Households generate pharmaceutical waste in the form of expired or unused medications, as well as empty pill bottles and other medication packaging.

Risk of pharmaceutical waste

Pharmaceutical waste poses a significant risk to the environment and human health. If not properly disposed of, pharmaceutical waste can contaminate soil and water supplies, and can also harm wildlife.

Environmental risks

- Antibiotic resistance: The release of antibiotics into the environment can contribute to the development of antibiotic-resistant bacteria (ARB). This is a major public health concern, as antibiotic-resistant infections can be difficult or impossible to treat [6].
- Endocrine disruption: Some pharmaceuticals, such as birth control pills and hormone replacement therapy drugs, can disrupt the endocrine system of animals and humans. This can lead to a variety of health problems, including reproductive disorders, developmental delays, and cancer [7].
- Aquatic toxicity: Some pharmaceuticals like Pharmaceutical and personal care products (PPCPs) can be toxic to aquatic life, even at low concentrations. This can harm fish, invertebrates, and other aquatic organisms [8].

Human health risks [7]

- Exposure to pharmaceutical waste can pose a risk to human health, particularly for vulnerable populations such as children and pregnant women.
- Children are more susceptible to the effects of pharmaceutical waste because their developing bodies are more sensitive to toxins.
- Pregnant women are at risk because exposure to pharmaceutical waste can harm their developing fetuses.

How to reduce the risk of pharmaceutical waste

There are a number of things that can be done to reduce the risk of pharmaceutical waste, including [9,10]:

- Proper disposal of unused and expired medications: Unused and expired medications should never be flushed down the toilet or thrown in the trash. Instead, they should be taken to a local pharmacy or hazardous waste collection facility.
- Use of generic medications: Generic medications are just as safe and effective as brand-name medications, but they are often less expensive. This can help to reduce the amount of unused and expired medications that are generated.
- Safe and responsible use of antibiotics: Antibiotics should only be used when prescribed by a doctor. Patients should take the full course of antibiotics, even if they start to feel better sooner. This helps to prevent the development of antibiotic-resistant bacteria.

Governments and healthcare organizations can also play a role in reducing the risk of pharmaceutical waste by developing and implementing policies and procedures for the proper management of pharmaceutical waste. This includes developing safe and effective methods for the disposal of pharmaceutical waste, and educating healthcare workers and the public about the importance of proper pharmaceutical waste disposal.

Disposal/treatment of pharmaceutical waste

The disposal/treatment of pharmaceutical waste is a complex issue, as pharmaceutical waste can contain a wide variety of chemicals, including hazardous waste. It is important to properly dispose of pharmaceutical waste to minimize its environmental and health risks.

Disposal methods for pharmaceutical waste [11,12]

- Incineration: Incineration is the most common method for disposing of hazardous pharmaceutical waste, such as cytotoxic drugs and sharps. Incineration involves burning the waste at high temperatures to destroy the pharmaceutical compounds.
- Landfilling: Landfilling is a suitable disposal method for non-hazardous pharmaceutical waste, such as expired or unused medications. However, it is important to note that landfills can leach contaminants into the environment over time.
- Wastewater treatment: Wastewater from pharmaceutical manufacturing plants and hospital pharmacies can be treated to remove pharmaceuticals and other contaminants. This can be done using a variety of methods, such as biological treatment, chemical treatment, and physical treatment.

Treatment methods for pharmaceutical waste

In addition to disposal methods, there are a number of treatment methods that can be used to reduce the environmental and health risks of pharmaceutical waste. These include:

- Advanced Oxidation Processes (AOPs): AOPs are a group of chemical processes that can be used to destroy pharmaceutical compounds in wastewater. AOPs work by generating free radicals, which are highly reactive species that can break down pharmaceutical compounds [13].
- Supercritical Water Oxidation (SCWO): SCWO is a process that uses high temperatures and pressures to destroy pharmaceutical compounds in wastewater. SCWO is a very effective treatment method, but it is also very expensive [14].
- Membrane filtration: Membrane filtration can be used to remove pharmaceutical compounds from wastewater. Membrane filtration works by passing the wastewater through a semipermeable membrane, which allows water molecules to pass through but blocks the larger pharmaceutical compounds [13].

Policies and strategies for removal and treatment of pharmaceutical waste

Policies and strategies for the removal and treatment of pharmaceutical waste vary from country to country. Pharmaceutical waste should be segregated from other types of waste. This is important to ensure that the pharmaceutical waste is properly disposed of and to avoid contaminating other waste streams. Pharmaceutical waste should be treated or disposed of in a manner that minimizes its environmental and health risks. This may involve incineration, landfilling, or wastewater treatment, depending on the type of waste and the applicable regulations. Policies and strategies should be developed and implemented in consultation with stakeholders, including healthcare professionals, waste management companies, and the public [14].

Some specific policies and strategies for the removal and treatment of pharmaceutical waste include [15,16]:

- Extended Producer Responsibility (EPR) programs: EPR programs make manufacturers responsible for the end-of-life management of their products. This can include the collection and disposal of pharmaceutical waste.

- Take-back programs: Take-back programs allow consumers to return unused or expired medications to pharmacies or other collection facilities. This helps to ensure that the medications are properly disposed of.
- Public education and awareness campaigns: Public education and awareness campaigns can help people to understand the importance of proper pharmaceutical waste disposal. These campaigns can also provide information about take-back programs and other disposal options.

Challenges:

There are a number of challenges associated with the removal and treatment of pharmaceutical waste. One challenge is the lack of harmonized regulations. Different countries have different regulations regarding the disposal of pharmaceutical waste, which can make it difficult for manufacturers and waste management companies to comply. Another challenge is the cost of treatment and disposal. Some treatment and disposal methods, such as incineration and SCWO, can be very expensive. This can make it difficult for developing countries to implement effective pharmaceutical waste management programs. Despite these challenges, there is a growing awareness of the need to properly manage pharmaceutical waste. Governments, healthcare organizations, and other stakeholders are working to develop and implement policies and strategies to reduce the environmental and health risks of pharmaceutical waste [17].

Methodical ways to neutralise pharmaceutical waste

Pharmaceutical waste neutralization is the process of making pharmaceutical waste less hazardous or toxic. This can be done through a variety of methods, including physical, chemical, and biological processes.

Physical methods [18]

- Shredding: Shredding breaks down pharmaceutical waste into smaller pieces, which makes it easier to treat and dispose of.
- Incineration: Incineration involves burning pharmaceutical waste at high temperatures to destroy the pharmaceutical compounds.
- Microwave irradiation: Microwave irradiation can be used to neutralize pharmaceutical waste by generating heat and destroying the pharmaceutical compounds.

Chemical methods [19]

- Oxidation: Oxidation involves using chemicals to break down pharmaceutical compounds into smaller, less toxic molecules.
- Neutralization: Neutralization involves using acids and bases to neutralize the pH of pharmaceutical waste, making it less hazardous.
- Precipitation: Precipitation involves using chemicals to form insoluble precipitates with pharmaceutical compounds, which can then be removed from the wastewater.

Biological methods

Biological methods of pharmaceutical waste neutralization involve using microorganisms to break down pharmaceutical compounds. This can be done in a variety of ways, such as using activated sludge processes, biofilm reactors, and constructed wetlands [20].

Sustainability in pharmaceutical development

Sustainability in pharmaceutical development refers to the incorporation of environmentally responsible practices and considerations throughout the entire lifecycle of a drug, from research and development to manufacturing, distribution, and eventual disposal. This approach aims to reduce the environmental footprint of the pharmaceutical industry while maintaining the quality and efficacy of medications. Key aspects of sustainability in pharmaceutical development include minimizing waste, conserving resources, and reducing energy consumption [21].

Green pharmacy practices

Green pharmacy practices encompass a range of strategies and initiatives aimed at making the pharmaceutical industry more environmentally friendly. Some examples of green pharmacy practices include [22]:

- Reducing chemical waste: Pharmaceutical manufacturers can minimize the use of hazardous chemicals and optimize processes to generate less chemical waste during drug production.
- Energy efficiency: Implementing energy-efficient technologies and practices in manufacturing facilities can significantly reduce energy consumption and greenhouse gas emissions.
- Sustainable sourcing: The pharmaceutical industry can adopt sustainable sourcing practices for raw materials, such as plant-based ingredients, to reduce the impact on natural ecosystems.

- Waste reduction: Reducing packaging waste and promoting recycling and reuse of pharmaceutical containers can contribute to a more sustainable approach.
- Eco-friendly solvents: Developing and using greener solvents in drug formulations can lessen the environmental impact of drug manufacturing.
- Biodegradable formulations: Exploring biodegradable drug formulations that break down in the environment can minimize the persistence of pharmaceuticals in ecosystems.
- Green chemistry principles: Applying principles of green chemistry, which focus on designing products and processes that are inherently safer and more sustainable, can help reduce the environmental impact of drug development.

Sustainable drug formulation and packaging [23]:

Sustainable drug formulation and packaging involve the development of pharmaceutical products that are more environmentally responsible. This includes:

- Reducing packaging waste: Using minimal and recyclable packaging materials to decrease the environmental impact of pharmaceutical packaging.
- Eco-friendly packaging materials: Exploring the use of eco-friendly materials, such as biodegradable plastics or materials from renewable sources, for drug packaging.
- Optimizing dosing: Formulating medications to be more concentrated or requiring smaller doses can reduce the overall amount of drug needed, leading to less waste.
- Extended-release formulations: Designing drugs with extended-release properties can reduce the frequency of dosing, minimizing packaging and waste over time.
- Eco-labels: Implementing eco-labelling and certification programs to inform consumers about the sustainability of pharmaceutical products.

Conclusion:

In conclusion, the proper management of pharmaceutical waste is of paramount importance to safeguard the environment, public health, and regulatory compliance. The risks associated with pharmaceutical waste, including environmental contamination, drug resistance, and public health hazards, necessitate methodical approaches for its removal, treatment, and neutralization. Effective policies, strategies, and methods have been established to address these risks, such as take-back programs, incineration, chemical neutralization, solidification, and more. Education and awareness are key components in ensuring that healthcare professionals and the public understand the importance of responsible pharmaceutical waste management. By adopting these methodical approaches,

we can work toward minimizing the adverse consequences of pharmaceutical waste and promoting a safer, more sustainable future for our communities and the planet.

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PHYTOCHEMICALS AS ANTI-DIABETIC AGENTS

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Abstract:

Diabetes is a significant, chronic illness that significantly affects the lives and overall health of individuals, families, and communities globally. It ranks among the top ten leading causes of adult mortality. The increasing medical challenges faced by patients with diabetes-related complications result in a substantial economic burden that could potentially hinder global economic growth in the near future. This underscores the inadequacies of the current healthcare system in effectively addressing the escalating impact of diabetes worldwide, emphasizing the urgent necessity for improved alternatives. A key challenge in diabetes treatment is to identify personalized factors that contribute to enhanced blood sugar control. Traditional plants have long been used as remedies for managing diabetes, producing various biologically active compounds with antidiabetic properties. This review aims to comprehensively document the current collection of herbal drugs used in the discovery and advancement of antidiabetic treatments. The ultimate goal is to offer a comprehensive repository of pharmacologically established antidiabetic phytoconstituents, with specific references to novel and cost-effective interventions, which may hold relevance for developing countries worldwide.

Keywords: Antidiabetic, Phytochemicals, Phytoconstituents, Herbal Drugs.

Introduction:

Diabetes mellitus is the prevalent hormonal ailment arising from issues with insulin secretion, insulin resistance, or both. It ranks as the third most prominent contributor to illness and death, following heart disease and cancer. Diabetes is a chronic medical condition stemming from insufficient insulin production by the pancreas or the body's reduced ability to use the insulin it produces. This malfunction revolves around insulin, a crucial hormone for regulating blood glucose levels. High blood sugar, referred to as hyperglycemia, is a common outcome of uncontrolled diabetes, progressively leading to

significant damage to various bodily systems, particularly the nerves and blood vessels [1]. At present, the global population of people affected by diabetes has surpassed 500 million. According to the IDF, it is anticipated that by 2045, approximately 1out of 8 adults will be contending with diabetes, indicating a more than 40% increase in prevalence compared to the current situation. [2]

Diabetes mellitus, marked by continual high blood sugar levels, encompasses a diverse range of disorders with various causes, affecting the human body at multiple organ levels. This complexity makes it challenging to adhere to a specific treatment plan. Managing this condition necessitates a multifaceted approach that should be tailored to each individual, acknowledging the need for personalized treatment strategies. Broadly, diabetes mellitus is categorized into two main types: type-1 and type-2. Type-1 diabetes is characterized by the absence of insulin production, resulting from the destruction of pancreatic β cells, whereas type-2 diabetes involves a gradual decline in insulin secretion by pancreatic β cells and reduced sensitivity of target tissues to this hormone's effects. Type 2 diabetes leads to various complications such as cardiovascular issues, nephropathy, neuropathy, and an increased susceptibility to infections [3,4].

This illustrates that the current healthcare system has typically been ill-prepared to address the escalating influence of diabetes worldwide, emphasizing the pressing necessity for more advanced and effective alternatives. The primary struggle within diabetic care revolves around pinpointing personalized factors that can contribute to enhanced management of blood sugar levels. In addition to traditional oral and injectable drugs, diabetes management involves dietary adjustments, regular physical activity, lifestyle modifications, weight management, and other supplementary treatments or complementary therapies like herbal remedies [5].

At present, a variety of medications for managing high blood sugar levels are accessible, operating notably by enhancing insulin sensitivity, supporting insulin function, boosting insulin production, and encouraging glucose absorption. However, certain antidiabetic drugs like metformin and sulfonylureas are associated with various undesirable effects such as diarrhea and lactic acidosis, as well as complications like hepatic failure, weight gain, rapid heart rate, and hypothyroidism [6]. Herbal medicine or botanical medicine refers to the use of plants for medicinal aims. The historical use of herbal medicine for treating and preventing various diseases, including diabetes, predates modern conventional medicine. Diabetes remains a significant global public health issue.

Plant-based substances like herbs possess the ability to lower blood glucose levels and improve diabetes with fewer negative effects. They accomplish this due to the existence of natural compounds such as flavonoids, saponins, alkaloids, tannins, glycosides, terpenes, and others [7].

The objective of this review is to emphasize the significance of herbal drugs in treating diabetes mellitus due to their bioactive plant compounds.

1. **Flavonoids** are plant metabolites that belong to a class of soluble polyphenolic compounds, characterized by two benzene rings linked by a brief three-carbon chain. Flavonoids found in nature are categorized into six classes: anthocyanidins, flavan-3-ols, flavonols, flavones, flavanones, and isoflavones. The potential antidiabetic effects of flavonoids are linked partially to their antioxidant capabilities and partly to their capacity to regulate certain cell signaling pathways. These dietary compounds are present in various sources such as fruits, vegetables, beverages, chocolates, herbs, and plants [8].
2. **Alkaloids** are considered secondary plant metabolites, are not only found in plants but also in bacteria, fungi, and other animals. They are natural compounds containing basic nitrogen atoms and are sometimes classified as a particular type of amines. Alkaloids have been identified as the active components in certain medicinal plants used for managing diabetes. The anti-diabetic effects of alkaloids involve enhancing GLUT 4 and glucokinase activity, as well as peroxisome PPARγ. Additional mechanisms include reductions in total cholesterol and triglyceride levels, attenuation of glucose-6-phosphatase activity, and improvement in hepatic glycogen content [9].
3. **Terpenoids,** also known as terpenes, are a diverse class of naturally occurring organic compounds derived from isoprene units. They are found in various plants and some animals, contributing to the characteristic scents and flavors of many herbs, spices, and essential oils. Terpenoids play essential roles in plant defense mechanisms and act as building blocks for more complex molecules such as steroids. They also exhibit various biological activities and have been studied for their potential medicinal properties. The conjugate of andrographolide-lipoic acid, a type of terpenoid, has shown potential for reducing blood sugar levels. Benzofuran-2-carboxaldehyde, an extracted hypoglycemic diterpene from *Globba pendula*, has displayed glucose-lowering properties. Similarly, the glucose-lowering effects of

clerodane diterpenoids have been documented. Stevioside and rebaudioside, diterpenes isolated from Stevia rebaudiana, possess anti-diabetic properties, with the translocation of Glucose Transporter 4 suggested as the mechanism of action [10, 11].

4. **Saponins,** significant plant metabolites, are naturally occurring glycosides that act as surfactants. They consist of sugar units linked to a hydrophobic aglycone, known as sapogenin, which can be either a triterpenoid or a steroid. Many medicinal plants with anti-diabetic properties owe their efficacy to saponins. For instance, the anti-diabetic effects of Anabasis articulate are attributed to the presence of saponins that stimulate insulin production. The saponin in Astragalus membranaceous is linked to the mitigation of oxidative stress and advanced glycation end product formation. Diosgenin, derived from Dioscorea rotundata, is known to enhance the activity of glucose-6-phosphate [12, 13].
5. **Tannin** is a type of polyphenolic compound found in natural sources such as berries, nuts, legumes, chocolate, spices, and herbs. There are three primary classes of tannins, including hydrolyzable tannins (e.g., gallic acid), non-hydrolyzable or condensed tannins (e.g., flavones), and phlorotannins (e.g., phloroglucinol). Tannins have been identified as the active anti-diabetic components in certain medicinal plants. Research has shown that tannic acid stimulates glucose transport and inhibits differentiation in 3T3-L1 adipocytes. This effect is achieved through the phosphorylation of the insulin receptor and the translocation of glucose transporter 4. Tannic acid also suppresses key genes involved in adipogenesis [14, 15].
6. A **glycoside** is a type of molecule that consists of a sugar molecule (the glycone) attached to a non-sugar moiety (the aglycone) through a glycosidic bond. Glycosides are commonly found in plants and are responsible for various biological activities. They often serve as a means of storing and transporting energy in plants. In some cases, they can also possess medicinal properties and play essential roles in traditional medicine and drug development. The anti-diabetic effect of Gymnema Sylvester was associated with the glycoside it contains. Similarly, bioactive flavonoid glycosides extracted from Jatropha curcus have demonstrated anti-diabetic properties in streptozotocin-induced diabetic rats. This active component works by reducing serum α-amylase and lactate dehydrogenase activities. Moreover, the extract regulates oxidative stress indicators like malondialdehyde [16, 17].

Isolated phyconstituents as antidiabetic agents:

1. **Apigenin:** This particular flavone flavonoid is commonly found in citrus fruits, onions, various vegetables, tea, and nuts. Its mode of operation involves enhancing antioxidant measures, promoting the translocation of glucose transporter 4, and preserving beta cells [18].
2. **Quercitin:** This flavonol flavonoid is found in onions, berries, apples, peppers, and coriander. Its anti-diabetic effects are demonstrated through the elevation of antioxidant enzymes, the reduction of lipid peroxidation, and the inhibition of intestinal glucose absorption by blocking GLUT2. Quercetin also obstructs tyrosine kinase and hinders cell proliferation [19].
3. **Daidzein,** an isoflavone flavonoid, is found in nuts, soybeans, and various fruits. It aids in enhancing lipid and glucose metabolism, improving insulin sensitivity, and promoting AMP-activated protein kinase phosphorylation in muscles [20].
4. **Rutin** can be found in oranges, grapes, buckwheat, lemons, limes, berries, and peaches. It enhances insulin secretion, replenishes glycogen content, reduces oxidative stress, inhibits the formation of advanced glycation end products, lowers glycosylated hemoglobin levels, and decreases pro-inflammatory cytokines such as IL-6 and TNFα. Additionally, it helps in restoring the antioxidant status of the liver [21].
5. **Chrysin** is a significant phytoconstituent has been extracted from various sources such as *Passiflora caerulea, Pelargonium peltatum, Tilia tomentosa*, bee pollen, honey, fruits, and vegetables. It has also been associated with reduced serum levels of Interleukin-1β and Interleukin -6. Due to these findings, chrysin is believed to have a preventive effect on nephropathy. Chrysin administration additionally contributes to improved insulin levels and reduced lipid peroxidation [22].
6. **Luteolin** has been recognized for its ability to enhance insulin activity and promote the transcriptional activation of PPARγ. It has also been documented to enhance insulin secretion. Luteolin is commonly found in significant quantities in various foods such as carrots, peppers, cabbage, apples, and a variety of vegetables and fruits [23].

Antidiabetic isolated phytoconstituents and their targeted metabolic pathways [24]

S. No.	Phytoconstitutent	Metabolic pathway as target
1.	Aegelin	Regeneration of pancreatic β cells and insulin secretion
2.	Berberin	Glucose transport, carbohydrate digestion and absorption
3.	Castanospermine	Carbohydrate digestion and absorption, insulin secretion
4.	Harmine,	Insulin secretion and β-cell regeneration
5.	Ferulic acid	Free radical scavenging activity, insulin secretion
6.	vinblastine, vincristine	Free radical scavenging action
7.	pinoline	Insulin secretion and β-cell regeneration
8.	Vicine	Insulin secretion
9.	Gymnemic acid	Regeneration of pancreatic β cells and insulin secretion
10.	Epigallocatechin-gallate	Free radical scavenging activity, insulinonematic activity
11.	Fenugreekine	Glucose transport, carbohydrate digestion and absorption
12.	Curcumin	Carbohydrate digestion and absorption, insulin secretion
13.	Stigmasterol	Regeneration of pancreatic β cells, insulin secretion

Conclusion:

Plants contain a multitude of chemical compounds known for their medicinal properties, which include alkaloids, flavonoids, glycosides, saponins, and more. These compounds are extracted from different parts of various plants, such as the roots, stems, leaves, flowers, fruits, and so on. The focus of this review is to compile and summarize the current understanding of the utilizations of plants and their derived constitutens for treating diabetes that target various metabolic pathways in the human body. Given their proven safety, effectiveness, and historical usage in various traditional medicinal systems, plant-based sources are considered to be safe. As a result, plants provide a natural alternative or supplement to conventional treatments, often with fewer adverse effects.

Nevertheless, to be formally recognized and utilized as drugs following strict pharmaceutical guidelines, further research is needed to assess their effects and potential benefits in the prevention and management of diabetes in humans. Numerous medications derived from plants have already been scientifically validated as effective treatments for diabetes. T he conventional approach to managing diabetes involves the use of synthetic antidiabetic medications that are readily accessible in the market. Despite their widespread use, these synthetic drugs are associated with various adverse effects, such as hypoglycemia, weight gain, increased cardiovascular risk, pancreatitis, hepatitis, heightened cancer risk, gastrointestinal complications, and the risk of developing lactic acidosis. The challenges and complications linked to the current synthetic medications have prompted researchers to explore alternative antidiabetic treatments derived from plants, which offer a more favorable safety and efficacy profile. Similar to the management of many other diseases, diabetes mellitus has long been addressed using plant-based remedies due to their notable effectiveness, reduced toxicity and side effects, affordability, and widespread availability. Phytochemicals that have been isolated are employed either as medicinal drugs or serve as chemical leads or models for creating biologically active compounds. The significant presence of phytochemicals in the pharmaceutical industry is evident when observing all the authorized drugs approved on a global scale [6, 24]. Numerous scientific studies have demonstrated the antihyperglycemic properties of these phytochemicals, making them effective in managing diabetic and metabolic complications, while avoiding the notable side effects often associated with conventional medications. While dietary and non-dietary plants have always been seen as promising sources of remedies for various health conditions, including diabetes, many plants and their bioactive constituents have not been extensively researched yet.

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PRECISION MEDICINE: TAILORING HEALTHCARE TO INDIVIDUALS

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Abstract:

Precision medicine represents a transformative paradigm in healthcare, pioneering in an era where medical treatments are customized to each individual's unique genetic, environmental, and lifestyle factors. This abstract explores the core principles and potential of precision medicine. At its heart, precision medicine recognizes that every patient is distinct, with genetic variations that affect their health and how they respond to treatments. By leveraging cutting-edge technologies like genomics, proteomics, and comprehensive patient data, precision medicine enables healthcare providers to identify specific genetic markers and molecular drivers of diseases. Armed with this information, healthcare professionals can develop personalized treatment plans that target the root causes of illnesses with greater precision, enhancing the efficacy of therapies and minimizing side effects. The impact of precision medicine is already evident in oncology, where therapies designed to target specific genetic mutations have led to remarkable improvements in patient outcomes. This groundbreaking approach, however, has broader applications. It has the potential to revolutionize the management of cardiovascular diseases, neurological disorders, rare genetic conditions, and various other ailments. Nevertheless, precision medicine is not without challenges, such as data security, ethical concerns, and equitable access to these advanced therapies. Despite these hurdles, the trajectory of precision medicine promises a healthcare landscape that is increasingly patient-centered, where individuals receive treatments tailored precisely to their unique biology, ultimately leading to better health outcomes and improved quality of life.

Keywords: Precision medicine, Individualized healthcare, Targeted therapy, Healthcare accessibility

Introduction:

Precision medicine:

Tailoring Healthcare to Individuals" heralds a groundbreaking shift in the realm of healthcare, fundamentally altering how medical treatments and interventions are conceived, developed, and administered. At its core, this innovative approach recognizes that each individual is biologically unique, with genetic, environmental, and lifestyle factors that significantly influence their health and responses to medical therapies. This introduction explores the essence and significance of precision medicine, shedding light on its transformative potential.

Precision medicine hinges on the belief that the one-size-fits-all approach to healthcare is outdated and inadequate. It embraces cutting-edge technologies like genomics, proteomics, and personalized diagnostics to unearth the specific genetic markers and molecular drivers underlying diseases. Armed with this knowledge, healthcare providers can craft personalized treatment plans that address the root causes of illnesses with unmatched accuracy, enhancing therapeutic effectiveness while minimizing adverse side effects.

The profound impact of precision medicine is already evident in oncology, where targeted therapies have significantly improved patient outcomes by honing in on specific genetic mutations. But its application extends far beyond cancer, with potential revolutions in the management of cardiovascular diseases, neurological disorders, rare genetic conditions, and various other maladies. Despite the remarkable promise of precision medicine, it introduces challenges such as data privacy, ethical considerations, and the equitable accessibility of these advanced therapies. Nonetheless, as technology advances and our understanding of human biology deepen, precision medicine is poised to take center stage in 21st-century healthcare. It heralds a future where healthcare is increasingly individualized; ensuring that each patient receives treatments precisely tailored to their unique biological makeup, ultimately leading to enhanced health outcomes and a superior quality of life. In following section important parameters are discussed.

Individualization of healthcare

Precision medicine is founded on the idea that every patient is unique, and their genetic, environmental, and lifestyle factors play a crucial role in their health. This approach moves away from the traditional one-size-fits-all model of healthcare.

Genetic profiling

Genetic fingerprinting or DNA profiling, is a technique that analyzes an individual's unique DNA to identify genetic variations, including DNA sequences and the number of repeats at specific loci. It is commonly used for various purposes, such as forensic investigations, paternity testing, and identifying genetic disorders. By comparing genetic profiles, scientists can determine relationships, establish identity, and assess the risk of inherited diseases. This powerful tool relies on the distinctiveness of an individual's DNA, making it a crucial tool in modern genetics and criminal justice. A central tenet of precision medicine involves the use of advanced genetic profiling to understand an individual's genetic makeup. By analyzing a patient's DNA, healthcare providers can identify specific genetic markers and variations that may influence their health and their response to treatments.

Targeted therapies

Targeted therapies are a cornerstone of precision medicine, which customizes treatment based on an individual's genetic and molecular profile. These therapies specifically target genes, proteins, or pathways responsible for a disease, such as cancer. By tailoring treatment to a patient's unique genetic alterations, targeted therapies aim to increase treatment effectiveness, minimize side effects, and improve overall outcomes. They are pivotal in the era of personalized medicine, offering more precise and efficient treatment strategies for a wide range of diseases. Precision medicine allows healthcare providers to develop highly customized treatment plans tailored to an individual's genetic profile. This approach aims to target the specific underlying causes of diseases with greater precision, enhancing treatment efficacy while minimizing the risk of adverse effects.

Technological advancements

The implementation of precision medicine heavily relies on cutting-edge technologies, including genomics, proteomics, bioinformatics, and data analytics. These technologies enable healthcare providers to acquire a comprehensive understanding of an individual's health and genetics.

Data security and privacy

Data security and privacy are critical in precision medicine. Personal health information, including genomic data, is highly sensitive. Robust security measures, like encryption and access controls, safeguard this data from unauthorized access or breaches. Privacy regulations, such as HIPAA, GDPR, and ethical guidelines, ensure that patient

information is handled with care. Anonymization and de-identification techniques protect patient identities. Striking a balance between sharing data for research and preserving patient privacy is a fundamental challenge in advancing precision medicine. Given the sensitivity of genetic and health data, ensuring data security and privacy is of paramount importance in precision medicine. Stringent data protection measures and ethical considerations are central to its implementation.

Patient-centered care

Precision medicine embodies a patient-centric approach that recognizes the significance of involving patients in decision-making, tailoring treatments to their specific needs, and providing a higher degree of care customization.

Challenges

Precision medicine faces several challenges, including equitable access to advanced treatments, ethical dilemmas related to genetic information, and the need for healthcare professionals to receive appropriate training in genomics and personalized medicine.

Expanding beyond oncology

While precision medicine has made a significant impact in oncology, it holds potential applications in other fields, such as cardiovascular diseases, neurological disorders, rare genetic conditions, and numerous other ailments.

Future prospects of precision medicine

Precision medicine holds promising future prospects, that will revolutionize healthcare in the coming years, are discussed in following section.

Personalized treatments

As genetic and molecular profiling becomes more accessible and affordable, customized treatments for individuals will increase. Tailored therapies based on a patient's unique genetic makeup will lead to more effective, targeted interventions.

Early disease detection

Precision medicine enables the identification of genetic markers and biomarkers for early disease detection, allowing for proactive and preventative healthcare strategies. This can significantly improve patient outcomes and reduce healthcare costs.

Pharmacogenomics

Advances in pharmacogenomics will lead to the development of drugs that are specifically matched to a patient's genetic profile. This will minimize adverse reactions and enhance drug efficacy.

Data integration and AI

Integration of patient data, including genomic, clinical, and environmental information, with the power of artificial intelligence will lead to more accurate disease risk assessment and treatment recommendations.

Rare disease research

Precision medicine will benefit individuals with rare diseases by identifying the underlying genetic causes and developing targeted therapies, providing hope for previously underserved patient populations.

Global collaboration

International cooperation and data sharing will facilitate larger-scale research and the discovery of novel treatments. Genomic databases and international networks will promote knowledge exchange and accelerate progress.

Ethical and regulatory frameworks

Continued development of ethical and regulatory guidelines is essential to address privacy concerns, consent issues, and equitable access to precision medicine.

Conclusion:

Precision medicine, a revolutionary approach in healthcare, aims to personalize medical treatments and interventions to suit individual patients based on their unique genetic, environmental, and lifestyle factors. This emerging field holds great promise for transforming healthcare outcomes. By tailoring treatments to each patient's specific needs, precision medicine has the potential to enhance therapeutic efficacy, minimize side effects, and improve patient satisfaction. Through genomic profiling and advanced diagnostics, healthcare providers can identify genetic predispositions and biomarkers associated with various diseases. This information allows for early detection and intervention, increasing the likelihood of successful treatment. Moreover, precision medicine can help target therapies for diseases like cancer, where individual tumor characteristics determine the most effective drugs and treatment strategies. However, implementing precision medicine on a broader scale requires addressing challenges such as data privacy, accessibility, and affordability. Additionally, healthcare professionals need specialized training to interpret genetic data and make informed treatment decisions. As technology continues to advance and data-sharing becomes more secure, precision medicine will likely play an increasingly pivotal role in improving healthcare outcomes and reducing the burden of disease on

individuals and society. The future of healthcare lies in tailoring treatments to individuals, maximizing the potential for better, more personalized care.

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TISSUE SYSTEM: EPIDERMAL TISSUE SYSTEM

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Introduction:

Living cell is the smallest unit of any living organism. The body of unicellular organism is composed of a single cell which performs all the activities like reproduction, absorption etc. whereas the body of multicellular organism is composed of many cells. The tissue is defined as the group of similar or dissimilar cells and performs the particular function. Every organ of plant is made up of different types of tissue. Each tissue performs a definite function. e.g.- The roots absorb water and minerals and conduct the same to the stem, it's branches and leaves. This is brought by the xylem, in order to perform this function adequately; the roots must be supplied with nourishment. The phloem tissues conduct the food material from the leaves to the root/different parts. Therefore, in higher plants, there is a definite division of labour. The tissues present in the different regions of a plant, carrying out similar physiological functions together form a system which is called a tissue system.

A group of tissue or tissues performing a similar function, irrespective of its position in the plant body form a tissue system.

Sachs (1875) recognized three tissue systems in the plants.

1. Epidermal tissue system: It includes the epidermis, cork layer and various outgrowths from the epidermal cells.
2. Fascicular (vascular) tissue system: It includes the vascular cylinder and is made up of two complex tissues (xylem and the phloem.)
3. Fundamental tissue system: It is also called the ground tissue system and includes those masses of tissue that have not been included in the first two systems.

In addition to systems for three basic functions mentioned above, it was later on discovered that, in plants, for specific functions, specialized tissues are formed. On the basis of physiological functions, Haberlandt classified the tissues into 12 different systems and from these the three important systems are:

A) Epidermal tissue system

B) Secretory tissue system

C) Mechanical tissue system

Epidermal tissue system:

The system of cells that lies on different plant parts and forms the outer covering or skin of plant body. The chief functions performed by these tissue systems are protection, absorption, secretion, excretion, gaseous exchange, reduces the rate of transpiration. This tissue system can be studied under three headings

1) Epidermis 2) Stomata 3) Various outgrowth from the epidermis

1) Epidermis: The word epidermis is derived from Greek words, ('epi' – upon and 'derma' -skin). It is outermost covering of various organs of plants such as roots, stems, leaves foliar structures, fruits and seeds.

a) **Single layered epidermis:** In most of the seed plants, the epidermis is single layered, called uniseriate e.g. bulb scale of onion. (Fig. 1)

b) Multiple epidermis: In some xerophytic plants the epidermis is composed of several layers of cells called multiseriate or multiple epidermis e.g. *Ficuselastica*, *Nerium*. This type of epidermis reduces the rate of transpiration and protects the underlying tissues. It lies on both the sides of lamina. The lower epidermis shows the presence of sunkenedstomta in cavities which are lined with many hygroscopic hairs (*Nerium*) (Fig. 2).

i) **Epidermal cells:** The epidermal cells are tubular, elongated, and thin walled. They are generally compactly arranged without intercellular spaces**.** They are variable in shapes and sizes. They form a continuous layer, which may be interrupted by stomata. The outer walls of the epidermal cells may be flat or convex or may show localized protuberances. The inner wall may be flat or convex or may bear conical projection. The epidermal cells are parenchymatous and living. The cells usually contain oils, tannins, and crystals of various types, anthocyanins and chloroplast (*Opuntia*, hydrophytes, and some ferns).

ii) Cuticle: This layer lies externalto the epidermis. It is made up of fatty substances called cutin. The thickness of cuticle varies in different plants and even in different organs of the same plant. It is very thin in shady plants and it is thick in the plants which are growing in dry condition or dry climate (Fig. 3).

In some plants the cuticle may be coated with wax which may be deposited in the form of granules (Plums and grapes), rods (sugarcane) hooked projection, scales or in the

form of smooth and homogenous layer**.** The active growing regions of the root do not possess cuticle. The cuticle reduces the rate of transpiration.

iii) Bulliform or motar cells: These cells are larger in size than the adjacent epidermal cells and have vacuoles. They may present anywhere in the leaf epidermis of monocot plants on both sides. These cells are characterized by-

i) They contain sufficient water and are turgid

ii) They lack solid contents

iii) Chloroplast may be present in some cases or absent

iv) The cell walls are made up of cellulose and pectic substances.

v) The outer walls are lined with cuticle

These cells play an important role in folding and unfolding of the developing leaves in monocot plants. When there is high light intensity and high temperature, the motor cells loose water and become flaccid, lamina start folding; on the contrary when there is low light intensity and low temperature, the motor cells receive water from the neighboring cells and become turgid, the lamina starts unfolding. This process protects the young leaves from the desiccations during dry and hot periods. (Fig. 4)

Maize leaf

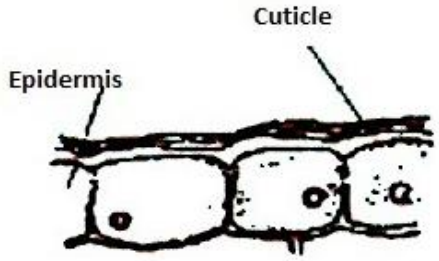


Figure 1: Uniseriate epidermis

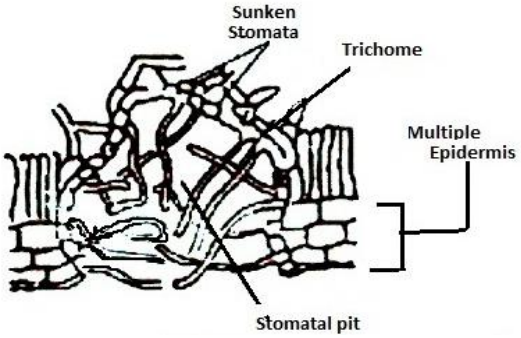


Figure 2: Multiple epidermis

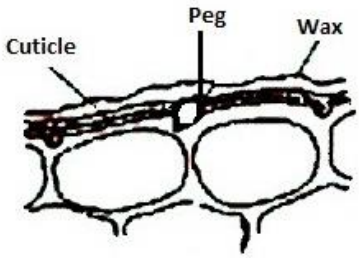


Figure 3: Cuticle (peg like)

e.g. Banana leaf

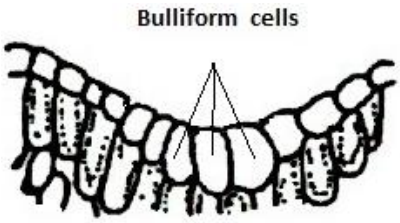


Figure 4: Bulliform cells

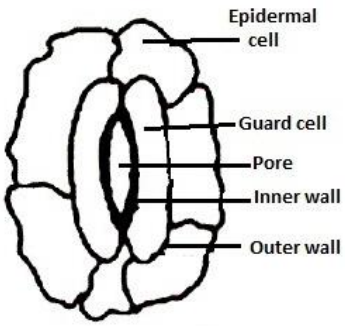


Figure 5: Structure of stomata

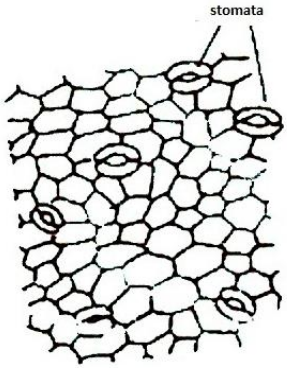


Figure 6: Scattered stomata

2) Stomata (Fig. 5)

These are minute apertures/openings found on the plant surface except the roots and are bounded by two guard cells. They are generally found in the epidermis of the leaves and younger parts of stem. They are absent in the roots and in the aerial parts of some plants like *Monotrapa, Neottia*. Each stoma has an opening which is guarded by two highly specialized epidermal cells called guard cells. The guard cells are bounded by two or more cells that are functionally associated with them are called the subsidiary or accessory cells. The stomata generally occur on the lower epidermis (hypostomatic leaf). In some plants (like- monocots), the stomata occur on both the surface of leaf (amphistomatic leaf). In the floating leaves e.g. *Nymphaea*, the stomata are found only on the upper epidermis (epistomatic leaf). In some xerophytes e.g. *Nerium,* the stomata are sunken. They are sunken in stomatal pits to check transpiration. They are restricted to the lower epidermis, the stomatal pit is lined with many hygroscopic hair (Fig. 5). In mesophytes, they lie with other epidermal cells. They are generally scattered in dicot leaves (Fig. 6). While they lie in rows in grass leaves (Fig. 7). The guard cells are living and contain chloroplast. They are mostly kidney shaped. The wall of the guard cell towards the pore is thicker than the outer wall away from the pore. This uneven thickness of the wall is useful in the movements of guard cells in opening and closing of stomatal pore.

Types of stomata

Metcalfe and Chalk (1950) classified stomata on the basis of their morphology into following types.

i) **Anomocytic type or ranunculaceous:** In this type, the stomata are surrounded by a limited number of cells that are similar in shape, size or form and cannot be distinguished from the rest of the epidermal cells. They have no subsidiary cells e.g. *Cucurbita* (Fig. 8).

ii) **Anisocytic type or cruciferous:** In this type of stomata, the guard cells are supported by three subsidiary cells of unequal sizes. Two are large and one is smaller e.g. *Petunia* (Fig. 9)

iii) **Paracytic type or rubiaceous:** In this type, the guard cells are supported by, two subsidiary cells with their long axis parallel to guard cells e.g. *Phaseolus* (Fig. 10).

iv) **Diacytic type or caryophyllaceous:** In this type, the guard cells are supported by a pair of subsidiary cells. The common wall of the subsidiary cells is at right angle to the guard cells. e.g. *Hygrophila* (Fig. 11)

v) **Graminaceous type:** In the member of the families Graminae (Poaceae) and Cyperaceae, the guard cells of the stomata are dumble shaped and are supported by *subsidiary* cells which are parallel to the long axis of the pole. (Fig. 12)

Stace (1965) recognized two more types:

Actinocytic type: in which the guard cells are surrounded by four or more subsidiary cells that are elongated radially to the guard cells. (Fig. 13)

Cyclocytic type: In which there are 4 or moresubsidiary cells which are arranged in the form of a ring around the guard cells.

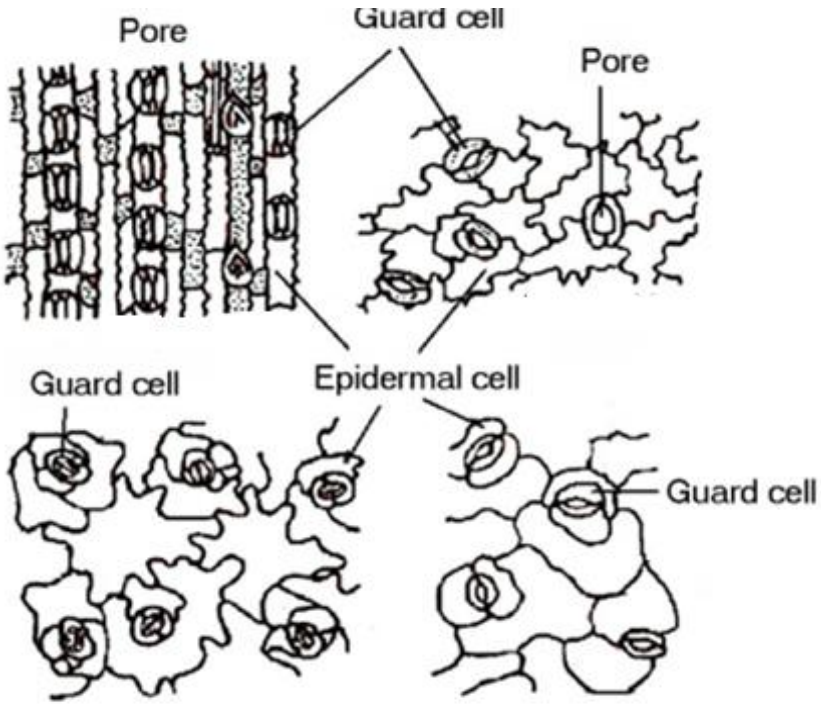


Fig. 7: Graminaceous stomata lie parallel e.g. Grass leaf;
Types of stomata: 8- Anomocytic type,
9- Anisocytic type, 10- Paracytic type

3) Epidermal outgrowth: These are the epidermal outgrowths developing from the epidermal cells. They can be studied under two heading: A) Trichomes B) Root hair.

A) Trichome: Trichome is a Greek word ('trichome' – hair). This term is used to designate various unicellular and multicellular outgrowths that originate from the epidermal cells. They are found on almost all plant parts and may be permanent or temporary features. Some of them remain alive throughout their existence on the epidermis, whereas some of them lose their protoplasmic contents and occur as dried structures. Foster (1949) classified these epidermal appendages/ outgrowths in to 4 main categories a) Hair b) Scales c) Colleters and d) Water vesicles.

a) Hair: The hair can be classified into two main categories-

i) Unicellular hair ii) Multicellular hair

i) Unicellular hair: (Fig. 11) Unicellular hairs are short, long or coiled, non septate, branched or unbranched in nature. They may be glandular or non glandular. The stinging hairs in *Urticadioca*are glandular. They arise from the lower epidermis of leaf and possess a poisonous secretion. In *Cannabis* the hair is long and hooked. In *Gossypiumarboreum* (Fig. 16) and *Verbena stricta* the hair is long and thick walled. They are sharply pointed. Unicellular trichomes show various shapes like clavate hairs, filiform hair (Fig. 12), 'Y' shaped (Fig. 13), 'T' shaped (Fig. 14), hooked hair (Fig. 15), water vesicle (Fig. 17).

Figure 11: Clavate hair

Figure 12: Filiform hair

Figure 13: Y shaped forked hair

Figure 14: T- shaped hair

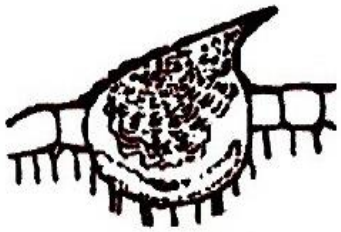
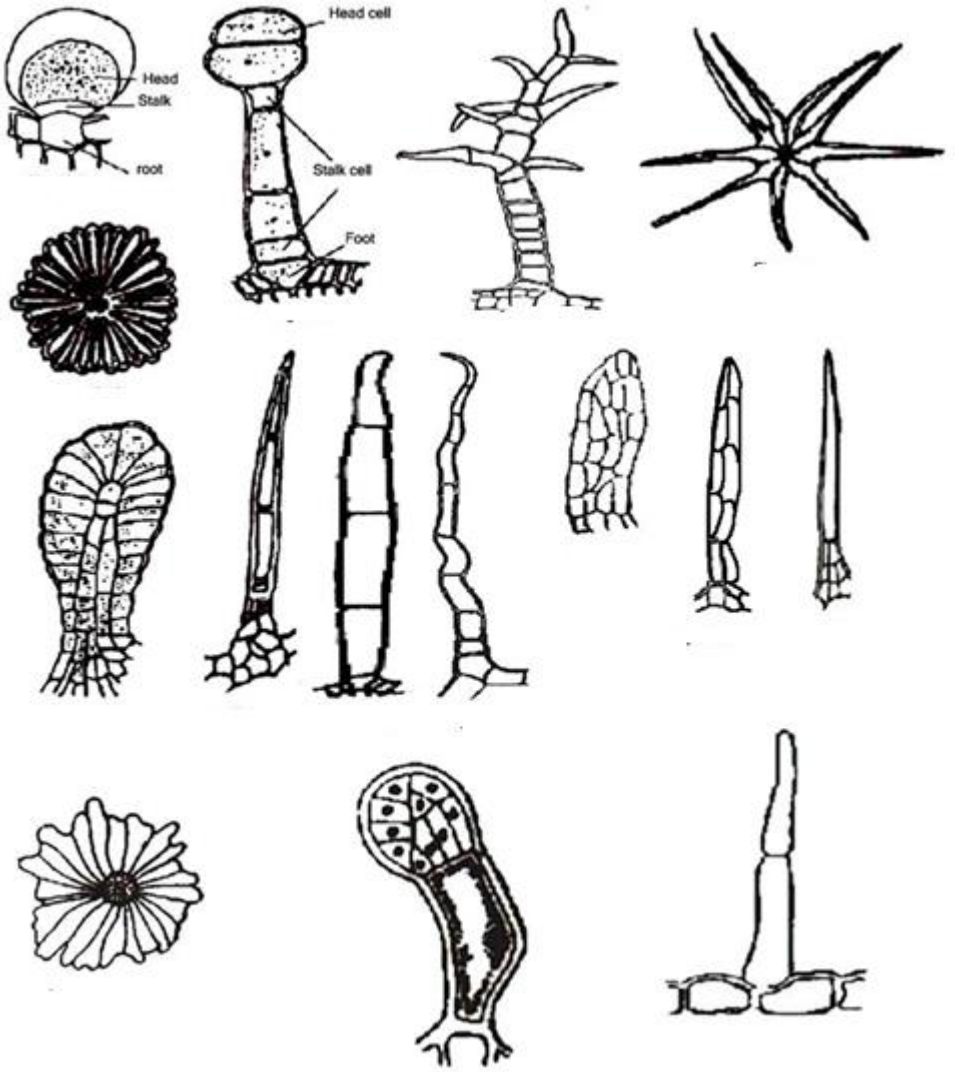


Figure 15: hooked hairs

Figure 16: unicellular hairs from the stem of cotton.

Figure 17: water vescicle

ii) Multicellular hair: They are made up of more than one cell. They may be short, long, branched and unbranched. They may be glandular or non-glandular. In different plants, the shape of the trichome may vary i.e. long, tubular. Peltate hair, stellate hair or vesicular, Dendroid hair, shaggy hair or colleter water vesicle, Filiform hair, Capitate hairs.



Multicellular Trichomes

The multicellular hair can be classified into uniseriate, biseriate and multiseriate.

The uniseriate, multicellular hairs are made up of a single row of more than one cell. It may have two celled OR many celled base. They may be short or long, branched or unbranched and glandular or non- glandular. They are two celled in *Leucasasper*, *Lantana.* They are long, pointed and many celled in *Tridax*. They are peltate in *Humulus.* In *Nymphaea*, *Geranium,* the leaves possess uniseriate multicellular and unbranched hairs that secrete mucilage. They are also called mucilage glands. The oil glands in Rutaceae also belong to this category.

Branched uniseriate hairs are found on the stem of *Withaniasomnifera.* They appear like like a small tree and are called dendroid hairs. Branched Stellate hair occurs on the stem of *Sida, Gossypium* and on the leaf petiole of *Solanummelongena, on the leaves of teak*. Biseriate multicellular hair occurs on the stem of *Lantana indica.* Multicellular, multiseriate hairs occur on the leaves of *Portulacaoleracea*.

The basal part of multicellular trichome is generally broad and remains embedded in epidermis. It is called foot. The upper part is relatively narrow and called body of trichome.

b) Scales: The peltatetrichome can be designated as scale e.g. *Olea*, *Humulus.*

c) Colleters: The trichome include all the unicellular and multicellular hair and peltate hair those are glandular in nature. They are found on foliage leaves e.g. *Nicotiana*, *Citrus, Urtica, Rhododendron.*

d) Water vesicle or bladders: These are bladder like or vesicular trichomes that are greatly swollen or distended epidermal cells, which generally store water. These are found in *Mesembryanthemumcrystallinum* (Ice plant).

B) Root hair: They are always unicellular, branched/ unbranched, living in nature and arise directly as lateral extensions of the epidermal cells of the root. The root hair cannot live long and die after a few days or few weeks.

Functions of epidermal tissue system:

1. Epidermis is an outermost covering (layer) of any plant organ which helps in protection of internal tissue against mechanical injuries.
2. Thick-walled epidermis and multilayered epidermis reduces the rate of transpiration i.e. prevent excessive evaporation of the water.
3. Epidermal cell acts as store house of water-(in the form of vesicles)
4. Epidermal cells when contain chloroplasts, they carryout photosynthesis and also concerned with secretion of some water etc.
5. Thick cuticle prevents the loss of water from the internal tissues in xerophytic plants.
6. The waxy bloom on the epidermis reflects sunlight and prevents heating of internal tissue
7. 7. Motor cells of the epidermis store water and avoid the rolling or folding of lamina due to the turgidity of motor cells.
8. Epidermis helps in gaseous exchange due to the presence of stomata

9. The root hair in root epidermis serves the function of absorption of water and minerals from the soils.

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PHYTOCHEMICAL SCREENING OF PLANT EXTRACTS REVEALED THE PRESENCE OF ALKALOIDS

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Abstract:

Medicinal plants are richest bio resource of drugs in traditional system of medicine and it also responsible for different colours, flavours and smell of plant. They also function as medicaments. These medicinal values of plants lie in some chemically active substance, that produce a definite physiological action on the human body. There are thousands of species of medicinal plants used globally for the cure of different infections. These plants are used as antimicrobial agents and several works have been carried out by scientists to find out its scientific basis. There is continuous and urgent need to discover new antimicrobial compounds with diverse chemical structures and novel mechanism of action because there has been an alarming increase in the incidence of new and re-emerging infectious diseases. Phytochemicals have two categories i.e., primary and secondary constituents. Primary constituents have chlorophyll, proteins sugar and amino acids. Secondary constituents contain terpenoids and alkaloids. Phytochemicals are known to possess antioxidant, antibacterial, antifungal, antidiabetic, anti-inflammatory, and radio-protective activity and due to these properties, they are largely used for medicinal purpose. The phytochemical screening of plant extracts revealed the presence of steroids, Saponin, alkaloids, flavonoids, glycosides, phenolic compounds, tannins, terpenoids and lignin. The phytochemical analysis of the plants is very important commercially and has great interest in pharmaceutical companies for the production of the new drugs for curing of various diseases. It is expected that the important phytochemical properties in the indigenous medicinal plants will be very useful in the curing of various diseases.

Keyword: Phytochemicals, Antioxidants, Medicinal Plants

Introduction:

The importance of medicinal plant in drug development is known to us and humans have used them for different diseases from the beginning of human history (Fransworth, 2008). Traditional folk treatment from wild plants has always guided researchers to search for novel medications to develop healthy life for humans and animals (Achterberg, 2013). In addition, some medicinal plants are still obscured within the plant which needs to be

scientifically evaluated. The medicinal plants are useful for healing as well as for curing of human diseases because of the presence of phytochemical constituents.

Phytochemicals are naturally occurring in the medicinal plants, leaves, vegetables and roots that have defense mechanism and protect from various diseases. Phytochemicals are primary and secondary compounds. Chlorophyll, proteins and common sugars are included in primary constituents and secondary compounds have terpenoid, alkaloids and phenolic compounds. Terpenoids exhibit various important pharmacological activities i.e., anti-inflammatory, anticancer, anti-malarial, inhibition of cholesterol synthesis, anti-viral and anti-bacterial activities (Wadood *et al.,* 2013, Santhi and Sengottuvel, 2016).

The bioactive constituents are present in *Momordica charantia* that is charantosides, momordin and goyaglycosides. It also includes terpenoids constituents such as momordicinin, momordenol, momordicin-28, momordicilin and momordol. *Morus nigra* is the botanical name of the mulberry and it belongs to the family Moraceae. Mulberries have shown various biological properties such as anti-inflammatory activities (Kim *et al.,* 1999). Guava is the common name of the *Psidium guajava* and it belongs to the family Myrtaceae. Its phytochemical study shows that its extracts have more than twenty compounds. *Prunus persica* belongs to the Rosaceae family. It is used as medicinal plants in African countries and this medicinal plant has shown strong anti-fungal activities (Caccioni *et al.,* 2002). Pomegranate is the common name of the *Punica granatum* (PG) and belongs to the family Lythraceae. It has much medical significance and used as medicines for centuries (Orak *et al.,* 2011).

Ephedra (*Ephedra intermedia*) belongs to family Ephedraceae and is a genus of nonflowering plants, related to Gnetales, very near relatives of angiosperms (Friedman, 1998). Majority of the 50 Ephedra species throughout the world are adapted as a shrub to moisture and desert conditions (Stevens 2003, Caveney *et al.,* 2001). Three species are found in Pakistan. *E. intermedia* shrubs are always green called Ma-Huang and, locally in Balochistan, they are called Oman. Ma-Huang (Ephedra) is resultant from the aerial parts of *Ephedra sinica Stapf, E. intermedia Stapf, E. equisetina Bunge*, and *E. distachya* L. It has been utilized medicinally as a stimulant, diaphoretic, and antiasthmatic (Huang, 1998). It is a xerophytic shrub plant and grows in unfavorable soil and climatic conditions such as high temperature and high light (Freitag and Maier-Stolte, 1989). Most of the marketed drugs of Ephedra extracts are taken from the ephedrine and pseudoephedrine alkaloids present in many species shoots. The best recognized drug prepared from Ephedra is Ma-Huang utilized in Chinese drugs for the treatment of nasal congestion, fever, and asthma (Zhu, 1998). These shrub plants also showed antioxidant and antimicrobial activities

(Parsaeimehr *et al.,* 2010). Ephedra basic compounds consist of the alkaloids ephedrine and pseudoephedrine and phenols (Nawwar, 1985). The stem consists of overall 1–3% alkaloids, having ephedrine comprising 30–70% of the total, depending on all the species and types of Ephedra plant. Ephedrine activates the CNS, increases the blood pressure, dilates the bronchial tubes, and increases the pulse rate. Pseudoephedrine is used for the relief of nasal congestion in its synthetic form (Inoko, 2009). HPLC method for the quantitative analysis (Imaz, 1993) can give a baseline resolution of the alkaloids with the advantage of simple extraction and direct analysis of the alkaloids without derivatives: the reversed-phase HPLC method (Yang and Wang, 1999)

Thus, main purpose of research work is to analyze the phytochemical screening and quantitative estimation of alkaloids and antioxidant activity of crude plant extract. The phytochemical analysis showed that the plant extract contains a mixture of phytochemicals as reducing sugars, cardiac glycoside, phenolic compounds, flavonoids, and alkaloids. The quantitative DPPH assay indicated that the plant extract has potent antioxidant activity which can be an excellent option for biological and chemical analysis and can be further subjected for the isolation of the therapeutically active compounds and the alkaloid content of PE in *E. intermedia* of Shairani (average 1.524 mg/500 mg) was higher than that in *E. intermedia* of Ziarat (average 1.36 mg/500 mg) and *E. intermedia* of Kalat (average 1.35 mg/500 mg), but the changeable range of total alkaloid content of each Ephedra was so broad that the whole alkaloid content ranges of these collected samples species really overlap, which cannot affect the claim that these Ephedra species should be analyzed as dissimilar drugs. The contents of PE and E are also pretty different between the samples of *E. intermedia*.

The recent studies have investigated that pomegranates are used for the treatment of a number of diseases e.g., diabetes, dysentery, diarrhea, cough, asthma, bleeding disorders, bronchitis, fever, AIDS, inflammation, ulcers, malaria, prostate cancer, hypertension, atherosclerosis, hyper lipidemia, male infertility, infant brain ischemia and obesity. *Fagonia cretica* (Zygophyllaceae) is one of the plants which are locally used in Pakistan as a cure of snake bite. *Acacia nilotica*, it is the member of the Leguminosae family. The subfamily of the Acacia nilotica is Mimosoideae (Brenan, 1983) Luffa cylindrica is the botanical name of the sponge gourds and belongs to Cucurbitaceae family. The fruits of this plant have flat seeds and black in colour which is enclosed by group of fibers. Medicinal and nutritional properties are the characteristics of Luffa cylindrical and seeds of this plant are used for curing of asthma, fever and sinusitis (Sashikala *et al.,* 2009). *Morus alba* is included in the Moraceae family. Their leaves and fruits are used for curing prematurely grey hair.

Its root bark is used by humans for more than 4 thousand years. Ficus palmate is included in the family of Moraceae and is used as dry vegetable. It is herbaceous perennial plant. Its leaves have hypotensive actions (Ayinde, 2007., Wadood *et al.,* 2013).

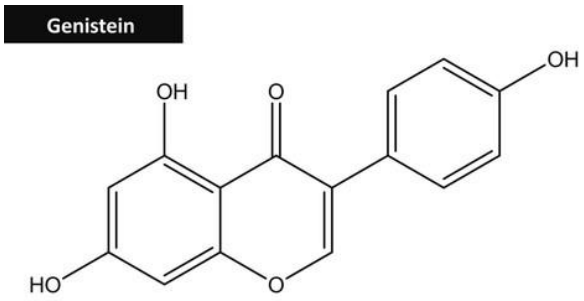

Figure 1: Phytochemical (Genistein)

Formation of oxidants

Oxygen, an essential element for life, can also be a reason for the destruction of tissue and/or impair its ability to function normally (Kehrer *et al.,* 1993). Oxidants or free radicals or oxygen-free radicals (OFR) or more generally called as reactive oxygen species (ROS) are formed due to various exogenous and endogenous factors. A free radical contains one or more unpaired electrons and is capable of independent existence. The formation of oxygen radicals could be the reason for the damaging effects of O2. A class of enzymes called superoxide dismutases (SODS) is responsible for the catalytic removal of superoxide free radical, O2 - (Lee *et al*., 2001). An average person has around 10,000–20,000 free radicals attacking each body cell every day. In some cases, ROS are produced specifically to serve essential biological functions, whereas in other cases, they are the byproducts of metabolic processes (Shigenaga *et al.,* 1994). Exogenous sources Exposure to radiation from the environment and manmade sources is the exogenous source for formation of oxidants. Low-wavelength electromagnetic radiation such as gamma rays splits water in the body to generate hydroxyl radical, OH -. The highly reactive OH - thus formed begins to react vigorously with the nearby cells (Halliwell, 1994). Even though OH - scavengers usually have rate constants more than 10 10 M -1 sec -1 for reaction with OH -, the most endogenous molecules react equally fast. The antioxidant systems that defend against damage by OH - do so by preventing its formation and by repairing the damage it causes (Timothy *et al.,* 2003). It has been estimated that 1-3% of the oxygen we breathe in is used to make O_2 -. Since humans consume large quantities of O_2, a simple calculation shows that over 2 kg of O_2 - is made in the human body every year-people with chronic inflammations may make much more (Halliwell *et al.,* 1994). These oxidants damage cellular

macromolecules, including DNA, protein and lipid (Fraga *et al.,* 1990) and accumulation of such damage may con-tribute to ageing and age-related diseases.

Endogenous sources and characteristics of oxygen radicals

Other than the exogenous sources such as exposure to radiation, enzymatically or non-enzymatically mediated electron transfer reactions are the source of free radicals produced in the cells. Electron leakage that occurs from electron transport chains, such as those in the mitochondria and endoplasmic reticulum, to molecular oxygen are the major source of free radicals (Fridovich, 1986). Oxidants are formed in the cells of our body mainly from the following four endogenous sources.

- ✓ Consumption of O_2 by mitochondria during normal aerobic respiration to produce H_2O. Oxidants such as oxygen free radical, H_2O_2 and hydroxyl radical are the byproducts of this process
- ✓ Destroying of bacteria and virus infected cells by phagogytic cells releases nitric oxide, hydrogen peroxide and oxygen free radical.
- ✓ Degradation of fatty acids and other molecules by peroxisomes, the organelles produce hydrogen peroxide as byproduct, which is then degraded by catalase.

The nondegraded peroxide gets into other compartments of nearby cell thereby leading to oxidative DNA damage (Ames *et al.,* 1993). When two free radicals a nonradical is produced due to the formation of covalent bond between their unpaired electrons. But a radical is formed when a free radical reacts with a nonradical and thus can initiate a chain reaction in the body. Oxidants produced during the course of p. 450 degra -dation of natural toxins. Organisms have developed many defense mechanisms to limit the level of reactive oxidants and the damage inflicted by them (Sang *et al.,* 2002). Despite the cell's anti- 3 oxidant defense system to counteract oxidative damage from free radicals, radical-related damage of DNA and proteins have been proposed to play a key role in the development of age-dependent diseases such as cancer, arteriosclerosis, arthritis, eurodegenerative disorders and others (Ames, 1989). Reactive oxygen species interacts with cellular components including DNA bases and forms damaged bases or strand breaks (Atoui *et al.,* 2005).

Antioxidants

Antioxidants are phytochemicals, vitamins and other nutrients that protect our cells from damage caused by free radicals*. In vitro* and *in vivo* studies have shown that antioxidants help prevent the free radical damage that is associated with cancer and heart disease. Antioxidants can be found in most fruits and vegetables but also culinary herbs and medicinal herbs can contain high levels of antioxidants. Dragland S and colleagues showed in their study entitled "Several Culinary and Medicinal Herbs are Important

Sources of Dietary Antioxidants", and published in the Journal of Nutrition (2003 May) that the antioxidant level of herbs can be as high as 465 mmol per 100 g. A study in 2006 by Thompson H J showed that a botanical diversity of fruits and vegetables plays a role in the biological effect of antioxidant phytochemicals. The consumption of smaller quantities of many phytochemicals may result in more health benefits than the consumption of larger quantities of fewer phytochemicals.

Antioxidants and its importance

Numerous studies with plant phytochemicals show that phytochemicals with antioxidant activity may reduce risk of cancer and improve heart health.

Antioxidants reduce the risk of cancer

Not all results are conclusive but many studies show that antioxidants may reduce the risk of cancer. A large randomized trial on antioxidants and cancer risk was the Chinese Cancer Prevention Study (1993). A combination of the antioxidants beta-carotene, vitamin E and selenium significantly reduced incidence of cancer. However, the Alpha-Tocopherol / Beta-Carotene Cancer Prevention Study (1994) showed that intake of beta-carotene increased lung cancer rates of male smokers.

Antioxidants protect the heart

Everyone knows that cholesterol causes heart diseases and tries to limit cholesterol intake. But a more important cause of fatty buildups in the arteries is the oxidation of low-density lipoprotein cholesterol. The use of dietary supplements of antioxidants could reduce the risk of cardiovascular disease, but there is no hard evidence. At this stage, studies only show that the intake of foods, naturally rich in antioxidants reduces this risk.

Antioxidant claims on foods

Antioxidants can be found in most foods, especially in fruits and vegetables, but we see more and more food products on the shelves with antioxidant claims. These antioxidant claims crop up everywhere: from beverages to chocolates. Food producers do this because of the very high consumer awareness of the term antioxidants. Consumers believe that a high intake of antioxidants will protect them from ageing, cancer, heart disease and other diseases. This awareness already started in the 1990s when mainly beverage producers launched so called ACE drinks, which contained the three antioxidant vitamins vitamin A, C and E. Now food producers are adding supper fruits such as red berries, pomegranate and acai. When the food producer claims antioxidants, they are mainly looking at the total content of antioxidants and not at their biological activity. The antioxidant activity of foods is mainly expressed as FRAP, ORAC or TEAC values, all of which are measured in a test tube. In future the antioxidant activity should be measured in humans, by determining the quantities absorbed in the blood and tissues.

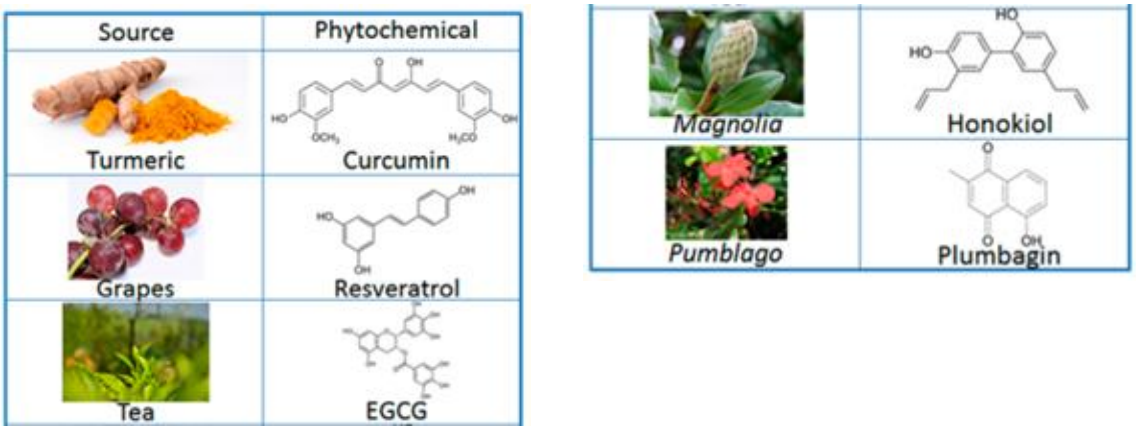

Figure 2: Source with Phytochemical

Table 1: Plants which are containing phytochemicals

Vegetables	**Fruits and Nut**	**Medicinal Plants**	**Beans and seeds**	**Common Herbs**	
Broccoli	Acai	Comfrey	Cacao	Aloe vera	Lemon Verbena
Fennel	Almond	Common Broom	Flaxseed	American Ginseng	Licorice
Garlic	Bilberry	Echinacea	Soy	Clary Sage	Marigold
Tomato	Black Raspberry	Ginkgo		Common Mallow	Milk Thistle
Wasabi	Blackberry	Goat's Rue		Common Yarrow	Red clover
	Blackcurrant	Lesser Celandine		Cornsilk	Rooibos
	Blueberry	Lungwort		Dandelion	Rosemary
	Cranberry	Opium Poppy		Ground Ivy	Sage
	Grape	Passion Fruit		Hawthorn	Schizandra
	Guarana	Periwinkle		Hop	Stinging Nettle
	Hazelnut	Red Bryony		Hyssop	Sweet Clover
	Mangosteen	Valerian		Indian Cress	Tea
	Maqui Berry	Wintergreen		Korean Ginseng	Verbena
	Noni			Lemon Balm	Wild Carrot

Source: salveolifesciences.com

Overdosage of antioxidants

Although some levels of antioxidants in the diet are required for good health, there is considerable doubt as to whether antioxidant supplementation is beneficial, and if so, which antioxidant is beneficial and in what amounts. Also, there is a risk of over consumption. Some antioxidants will act as pro-antioxidants when consumed in high quantities and in combination with factors such as exposure to pollution, smoking and excessive exercise. One famous study called the "Alpha Tocopherol, Beta Carotene Cancer Prevention Study", tried to determine whether taking vitamin E and beta carotene daily reduced the risk of lung cancer. In this study 18% more lung cancers developed in the people taking the antioxidant supplements, the opposite of what the researchers expected.

Antioxidants and risk of stroke

Stroke remains one of the main causes of death and morbidity worldwide. Epidemiological studies indicate that environmental factors, such as diet, play a role in the risk of stroke. Fruits and vegetables are our main dietary suppliers of antioxidants, and some contain high levels of popular antioxidants ascorbic acid, beta-carotene and vitamin E. Randomized controlled studies investigating the effect of the intake of these three antioxidants as supplements have failed to find a reduction in stroke. But fruits and vegetables are also rich sources of a broad range of phytochemicals, most of which have strong antioxidant capacities. Antioxidants may reduce the process of atherosclerosis by neutralizing free radicals, but also by improving the endothelial function, lowering blood pressure and reducing inflammation.

Study results

Lead author Daniele Del Rio from the University of Parma, Italy, reported in the Journal of Nutrition that antioxidants may play a role in reducing the risk of cerebral infarction. The study investigated the relation between dietary total antioxidant capacity and risk of ischemic and hemorrhagic stroke in 41,620 men and women. They also found that a high intake of vitamin E could be positively associated to the risk of brain hemorrhagic events.

A more recent study found that the more antioxidants a woman eats the less chance that she will suffer from stroke. For this study, Wolk and co-workers used the results of the large Swedish Mammography Cohort that included 36,715 women who were followed during a period of about 11 years. In the group of women who had no cardiovascular disease at baseline, those with the highest intake of antioxidants had a 17% lower risk of total stroke when compared with those with the lowest intake. The study concluded that total antioxidant capacity of the diet may be of importance for the prevention of stroke among women free from cardiovascular disease and for the prevention of hemorrhagic stroke among women with a history of cardiovascular disease.

Phytochemicals as candidate nutrients

Without specific knowledge of their cellular actions or mechanisms, phytochemicals have been considered possible drugs for millennia. For example, Hippocrates may have prescribed willow tree leaves to abate fever. Salicin, having anti-inflammatory and pain-relieving properties, was originally extracted from the bark of the white willow tree and later synthetically produced to become the staple, over-the-counter drug aspirin (Sneader, 2000). Specific phytochemicals, such as fermentable dietary fibers, are allowed limited health claims by the US Food and Drug Administration (FDA).

Clinical trials and health claim status

Phytochemical-based dietary supplements can also be purchased. According to the American Cancer Society, "Available scientific evidence does not support claims that taking phytochemical supplements is as good for long-term health as consuming the fruits, vegetables, beans, and grains from which they are taken."

How do phytochemicals work?

There are many phytochemicals and each works differently. These are some possible actions:

- **Antioxidant** - Most phytochemicals have antioxidant activity and protect our cells against oxidative damage and reduce the risk of developing certain types of cancer. Phytochemicals with antioxidant activity: allyl sulfides (onions, leeks, garlic), carotenoids (fruits, carrots), flavonoids (fruits, vegetables), polyphenols (tea, grapes).
- **Hormonal action** - Isoflavones, found in soy, imitate human estrogens and help to reduce menopausal symptoms and osteoporosis.
- **Stimulation of enzymes** - Indoles, which are found in cabbages, stimulate enzymes that make the estrogen less effective and could reduce the risk for breast cancer. Other phytochemicals, which interfere with enzymes, are protease inhibitors (soy and beans), terpenes (citrus fruits and cherries).
- **Interference with DNA replication** - Saponins found in beans interfere with the replication of cell DNA, thereby preventing the multiplication of cancer cells. Capsaicin, found in hot peppers, protects DNA from carcinogens.
- **Anti-bacterial effect** - The phytochemical allicin from garlic has anti-bacterial properties.
- **Physical action** - Some phytochemicals bind physically to cell walls thereby preventing the adhesion of pathogens to human cell walls. Proanthocyanidins are responsible for the anti-adhesion properties of cranberry. Consumption of cranberries will reduce the risk of urinary tract infections and will improve dental health.

Table 2: A different type of phytochemical (Source: salveolifesciences.com)

Alkaloid 1. Caffeine 2. Theobromine 3. Theophylline	Hydroxycinnamic Acids 1. Chicoric acid 2. Coumarin 3. Ferulic acid 4. Scopoletin	Monoterpenes 1. Geraniol 2. Limonene
Anthocyanins 1. Cyanidin 2. Malvidin	Isoflavones 1. Daidzein 2. Genistein	Organosulfides 1. Allicin 2. Glutathione 3. Indole-3-Carbinol 4. Isothiocyanates 5. Sulforaphane
Carotenoids 1. Beta-Carotene 2. Lutein 3. Lycopene	Lignans 1. Silymarin	Xanthophylls 1. Astaxanthin 2. Beta-Cryptoxanthin
Coumestans Flavan-3-Ols Flavonoids 1. Epicatechin 2. Hesperidin 3. Isorhamnetin 4. Kaempferol 5. Myricetin 6. Naringin 7. Nobiletin 8. Proanthocyanidins 9. Quercetin 10. Rutin 11. Tangeretin	Monophenols 1. Hydroxytyrosol	Phenolic Acids 1. Capsaicin 2. Ellagic Acid 3. Gallic acid 4. Rosmarinic acid 5. Tannic Acid
Phytosterols 1. Beta-Sitosterol	Saponins Stylbenes 1. Pterostilbene 2. Resveratrol	Triterpenoids 1. Ursolic acid
Other Phytochemicals 1. Damnacanthal 2. Digoxin 3. Phytic acid		

Qualitative and Quantitative Phytochemical analysis in the plants

A. Preparation of plant extract

The leaves of the selected plants were removed from the plants and then washed under running tap water to remove dust. The plant samples were then air dried for few days and the leaves were crushed into powder and stored in polythene bags for use. The plant powder was taken in a test tube and distilled water was added to it such that plant powder soaked in it and shaken well.

The solution then filtered with the help of filter paper and filtered extract of the selected plant samples were taken and used for further phytochemical analysis (Santhi and Sengottuvel, 2016).

B. Qualitative phytochemical analysis

Preliminary phytochemical analysis was carried out for the extract as per standard methods described by Brain and Turner (1975) and Evans (1996).

Detection of alkaloids

Extracts were dissolved individually in dilute hydrochloric acid and filtered. The filtrates were used to test the presence of alkaloids.

Mayer's test: Filtrates were treated with Mayer s reagent. Formation of a yellow cream precipitate indicates the presence of alkaloids.

Wagner's test: Filtrates were treated with Wagner s reagent. Formation of brown/ reddish brown precipitate indicates the presence of alkaloids.

Detection of Flavonoids

Lead acetate test: Extracts were treated with few drops of lead acetate solution. Formation of yellow colour precipitate indicates that the presence of flavonoids.

H_2SO_4 test: Extracts were treated with few drops of H_2SO_4. Formation of orange colour indicates that the presence of flavonoids.

Detection of steroids

Two ml of acetic anhydride was added to five mg of the extracts, each with two ml of H_2SO_4. The colour was changed from violet to blue or green in some samples indicate that the presence of steroids.

Detection of terpenoids

Salkowski's test

Five mg of the extract of the leaves, flowers and seeds was mixed with two ml of chloroform and concentrated H_2SO_4 (3ml) was carefully added to form a layer. An appearance of reddish brown colour in the inner face was indicates that the presence of terpenoids.

Detection of anthroquinones

Borntrager's test

About five mg of the extract was boiled with 10% HCl for few minutes in a water bath. It was filtered and allowed to cool. Equal volume of $CHCl_3$ was added to the filtrate. Few drops of 10% NH_3 were added to the mixture and heated. Formation of pink colour indicates that the presence anthroquinones.

Detection of phenols

Ferric chloride test: 10mg extracts were treated with few drops of ferric chloride solution. Formation of bluish black colour indicates that the presence of phenol.

Lead acetate test: 10mg extracts was treated with few drops of lead acetate solution. Formation of yellow colour precipitate indicates that the presence of phenol.

Detection of saponins

About 0.5mg of the extract was shaken with five ml of distilled water. Formation of frothing (appearance of creamy miss of small bubbles) shows that the presence of saponins.

Detection of tannins

A small quantity of extract was mixed with water and heated on a water bath. The mixture was filtered and ferric chloride was added to the filtrate. A dark green colour was formed. It indicates that the presence of tannins.

Detection of carbohydrates

0.5mg extracts were dissolved individually in five ml distilled water and filtered. The filtrate was used to test the presence of carbohydrates.

Detection of protein & amino acids

Biuret test: To 0.5 mg of extract equal volume of 40% NaOH solution and two drops of one percent copper sulphate solution was added. The appearance of violet colour indicates that the presence of protein.

Ninhydrin test: About 0.5 mg of extract was taken and two drops of freshly prepared 0.2% Ninhydrin reagent was added and heated. The appearance of pink or purple colour indicates that the presence of proteins, peptides or amino acids.

Detection of oils and resins

Test solution was applied on filter paper. It develops a transparent appearance on the filter paper. It indicates that the presence of oils and resins.

Quantitative determination of secondary metabolites:

Estimation of alkaloids: Alkaloids were determined using Harborne method (Harborne 1980). Five grams of the sample was weighed into a 250 ml beaker, 200 ml of 10% acetic

acid in ethanol was added and covered and allowed to stand for 4 h. This was filtered and the extract was concentrated on a water bath to one quarter of the original volume. Concentrated ammonium hydroxide was added drop wise to the extract until the precipitation was complete. The whole solution was allowed to settle and the precipitate was collected and washed with dilute ammonium hydroxide and then filtered. The residue is the alkaloid, which was dried and weighed.

Estimation of flavonoids: The total flavonoid content in the sample was estimated by the method of Chang 2002. A volume of 0.25 ml of the sample was diluted to 1.25 ml with distilled water. 75 µl of 5% sodium nitrite was added and after six minutes 0.1 5 ml of aluminium chloride solution was added. 0.5 ml of 0.1M NaOH was added after 5 min and made up to 2.5 ml with distilled water. The solution was mixed well and the absorbance was read at 510 nm along with standard quercetin at 5 - 25 µg concentration. The results are expressed as mg of flavonoids as quercetin equivalent / gm of dried sample.

Total Phenolic Content (TPC): Total phenolic content of extract was determined according to the Folin-Ciocalteau method (Slinkard and Singleton1977) with some modifications. Briefly, 0.1 ml of extract (200, 600 and 1000 µg/ml), 1.9 ml distilled water and 1 ml of Folin - Ciocalteau's reagent were seeded in a tube, and then 1 ml of sodium carbonate was added. The reaction mixture was incubated at 25 °C for 2 h and the absorbance of the mixture was read at 765 nm. The sample was tested in triplicate and a calibration curve with six data points for catechol was obtained. The results were compared with catechol calibration curve and the total phenolic content of sample was expressed as mg of catechol equivalents per gram of extract.

Total Tannins Content (TTC): Tannins - phenolics were determined by the method of Peri and Pompei 1971). 1 ml of the sample extracts of concentration 1mg/ml was taken in a test tube. The volume was made up to 1ml with distilled water and 1 ml of water serves as the blank. To this 0.5 ml of Folin's phenol reagent (1:2) followed by 5ml of 35% sodium carbonate was added and kept at room temperature for 5 min. Blue colour was formed and the colour intensity was read at 640 nm. A standard graph (gallic acid - 1 mg/ml) was plotted, from which the tannin content of the extract was determined. The total tannin content was expressed in mg/g of extract.

Total saponins: The fruit extract was ground and 20 g of extract put into a conical flask and 100 ml of 20% ethanol is added to the sample (Obadoni and Ochuko 2002):. The sample is heated over a hot water bath for 4 h with continuous stirring at about 55 ºC. The mixture is then filtered and the residue re-extracted with another 200 ml of 20% ethyl alcohol. The combined extracts are reduced to 40 ml over a water bath at about 90 ºC. The

concentrate is then transferred into a 250 ml separating funnel and 20 ml of diethyl ether is added to the extract and vigorously shaken. The aqueous layer is recovered while the diethyl ether layer is discarded and the purification process is repeated. 60 ml of n-butanol is added and the combined n-butanol extracts is washed twice with 10 ml of 5% sodium chloride. The remaining solution is then heated in a water bath and after evaporation; the samples are dried in the oven to a constant weight and values are expressed as mg/g of extract.

Determination of flavonoids by HPLC method: HPLC was carried out by the method of Hertog et al., 1992 For the purpose of determining flavonoids. The coloumn used is C18 equipped with pump (LC-10AT VP1), SIL-6A automatic injector, and detector (SPD-10AVP) set as 370 nm. The sample extract was injected into the loop and the temperature was maintained at 40 ºC and mobile phase consist of 50ml of methanol, 1ml of water, and 50ml of phosphoric acid (100:100:1) with the flow rate of about 1.5 mL/ min. The flavonoids were expressed as mg/g of fresh weight.

Determination of minerals elements: The minerals were determined by the dry ash extraction method using atomic spectrometry.

Phytochemicals in greenery food had great deals of attraction. Mainly on their role in preventing diseases caused and the result of oxidative stress, and release reactive oxygen species has single oxygen of various radicals as a damaging side effect of aerobic metabolism. The detailed information of phytochemicals in various solvent are used to the process of are shown in the above mention tables. This paper mainly revealed to the phytochemical as secondary metabolite and they can be used to the pharmaceutical industry for producing an efficient drug. This study indicating result of the above medicinal plants gives a basis of application in traditional medicine, and also contain some bioactivity of phytochemical constituents was more valuable. Qualitative analysis of photochemical was more interesting area and also important application of biomedical in pharmaceutical industries. This phytochemical analysis was very useful finding chemical compound in the plant material that led to their quantitative estimation and locating the pharmacy field (Mojab *et al.,* 2003; Rajasekar and Hemalatha, 2015).

Quantitative analysis showed that ethanolic extract contains higher amounts than other two extracts (aqueous and ethyl acetate extract). From the findings of the study it may be concluded that the ethanolic extract of *plant extract* acts as the potential source of phytochemical which may be used traditional medicine for prevention of several diseases

Conclusion:

Medicinal and aromatic plants are potential source of raw materials used for manufacture of drugs and perfumery products more than a quarter of all the medicines used in the world today contain natural compounds derived from plants that often serve lead molecules whose activities can be enhanced by manipulation through combinations with chemicals and by synthetic chemistry that can be exploited in the field of new drugs research and development. The primary benefits of using plants derived medicines are that they are relatively safer than synthetic alternatives offering profound therapeutic benefits and more affordable treatment. Phyto constituents are the natural bioactive compounds found in plants. This phyto-constituents work with nutrients and fibers to form an integrated part of defense system against various diseases and stress conditions. Phyto chemicals are basically divided into two groups, i.e. primary and secondary constituents; according to their functions in plant metabolism. Primary constituents comprise common sugars, amino acid, proteins and chlorophyll while secondary constituents consist of alkaloids, terpenoid, steroids and flavonoids, so on.

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A CONCISE REVIEW ON PHYTOCHEMICALS

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Abstract:

Medicinal plants and herbal preparations are currently attracting significant attention from scientific communities due to their consistent pharmacological activities, accessibility to the general public, and efficacy in treating a wide range of illnesses. The bioactivity of natural products is associated with the effects of various phytochemicals such as alkaloids, tannins, terpenoids, cardiac glycosides, saponins, flavonoids among others. Either as the pure compounds or as standardized plant extracts, phytochemicals provide unlimited opportunities for new drug leads. The phytochemicals are known to have several properties important to cells including; prophylactic, therapeutic, nutritive and immune-modulative properties.

Keywords: Phytochemicals, Alkaloids, Flavonoids, Pharmacological Actions, Therapeutic Properties.

Introduction:

Phytochemicals are natural bioactive compounds synthesized in plants that appear to have important physiological impacts in the human body. They cover a broad range of chemical substances such as, alkaloids, flavonoids, polyphenols, saponins, steroids, vitamins, among others. Depending on their role in plant metabolism they are divided into two types viz Primary and secondary metabolites (Rex *et al.,* 2018). Sugars, amino acids, proteins, chlorophyll etc. are examples of primary metabolites whereas, the secondary metabolites include flavonoids, alkaloids, terpenoids, saponins, tannins and phenolic compounds. The therapeutic properties of plants are due to phytochemicals, which have variety of physiological effects on the human body (Savithramma *et al.,* 2011).

Functions of phytochemicals in the living organisms

Phytochemicals carry out a number of functions in the living organisms and the mechanism by which they perform it has not been completely understood. The important functions of phytochemical are:

1. They acts as antioxidants and prevents the oxidative damage of key biomolecules including nucleic acids, proteins, and fats.
2. They function as antimicrobial agents and can be used as antibacterial, antiviral, antifungal, anti-trypanocidal agents.
3. They stimulate the immune system.
4. They carry out the modulation of various detoxifying enzymes.
5. They shows anti-inflammatory effects and decreases aggregation of platelets.
6. Interfere with the binding of pathogens to cell receptors.

Their other activities include antidiarrheal, antihelminthic, antimalarial, anti-atherosclerosis, anti-allergy, hepatoprotective, antidiabetic, antimutagenic, pain relief, wound healing, and antihypertension. Phytochemicals are also utilized in appetite enhancement, in the treatment of cough, toothache, sore throat, ulcers, menstrual bleeding, enhancement of sperm count, dysentery treatment, stomach abnormality and vertigo. Numerous additional functions of phytochemicals exist depending on the plant. Approximately 80% of the world utmost valuable drugs are from plants (Egbuna *et al.,* 2018).

Sources of phytochemicals

Phytochemicals are present in fruits, vegetables, legumes, whole grains, spices, herbs, shrubs as well as trees. They get accumulated in different plant parts for instance in the leaves, fruit, bark, stem, seeds, roots, and flowers at varying concentrations. Certain phytochemicals are also produced by other living beings for example fungi, even though the mechanism by which they synthesize it might vary. With the exception for some refined foods for instance sugar or alcohol several foods containing phytochemicals are already part of our regular diet. Eating at least five to nine servings of rainbow-colored fruits or vegetables each day is the simplest method to increase the intake of phytochemicals (Egbuna *et al.,* 2018).

Classification of phytochemicals

There are thousands of different phytochemicals. Since there are so many of them and new phytochemicals are discovered so quickly, there hasn't been a consistent classification scheme. The important phytochemicals are: Alkaloids, Anthocyanins, Coumarins, Flavonoids, Fatty acids, Lactones, Polypeptides, Polyphenols, Tannins, Terpenoids, Saponins, Sterols

Alkaloids

Alkaloids are a class of secondary metabolites that occur naturally in plants and are mostly composed of basic nitrogen atoms. They are among the most diverse, effective, and important plant compounds from a medicinal standpoint. Currently, there are about 5,500 alkaloids known (Roy, 2017). The majority of alkaloids taste bitter. Depending on the sort of heterocyclic ring structure a molecule contains, alkaloids are divided into different categories including steroidal, diterpenoid, pyrrolidine, pyridine, indole, quinoline, isoquinoline, quinazoline and other alkaloids. Each of these groups is subdivided into a number of subgroups based on the structural features of its representatives (Ahmed Shakil, 1998). They protect plants against micro-organisms by showing antibacterial and antifungal properties, insects and herbivores by feeding deterrence and also against other plants by secreting allelopathic substances (Molyneux *et al.,* 1996). The majority of alkaloids are distinct crystalline substances that combine with acids and form salts. They may present in the plant in their free form, as salts, or as N-oxides. Most alkaloids contain oxygen in addition to carbon, hydrogen, and nitrogen. Some of them are liquids without oxygen, such as nicotine from tobacco and coniine from hemlock. Despite being very uncommon, colourful alkaloids do exist; for example, berberine is yellow and the salts of sanguinarine are copper-red (Evans, 2009). A number of these compounds shows strong pharmacological effects. As an illustration, well-known plant alkaloids include the narcotic analgesics codeine and morphine, apomorphine which is a derivative of morphine is used in Parkinson's disease, papaverine is used as the muscle relaxant, and the antimicrobial drugs berberine and sanguinarine. Additionally, some effective anti-cancer drugs have been made from plant compounds (Kaisa *et al.,* 2011; Sarah 2010; Bribi, 2018). The alkaloid berberine shows cardioprotective, immunoregulative, anti-HIV, anti-fungal, anti-malarial, anti-inflammatory, antioxidant, anti-mutagenic, cerebro-protective, vaso-relaxing, and analgesic properties (Zuo *et al.,* 2006).

Flavonoids

The flavonoids are derived from flavone and contain two benzene rings separated by a propane unit. They are commonly water-soluble compounds. (Williams and Grayer, 2004). Flavonoids are polyphenolic compounds that are abundant amid vascular plants and present as glucosides, aglycones, and methylated derivatives. The six-membered ring which condensed with the benzene ring is either pyrone which is found in flavones and flavonols or its dihydro derivative which is found in flavanones and flavan-3-ols. The

flavonoids are of two classes: flavone and isoflavone depending upon the position of the benzenoid substituent. A large number of flavonoids found in conjugated form naturally associated with sugar and, within any one class, may be classified as monoglycosidic, diglycosidic, etc. At position 3 or 7 the glycosidic linkage is usually present and the carbohydrate unit can be D-glucose, L-rhamnose, galactose or arabinose (Pretorius JC, 2003). Additional oxygen-containing heterocyclic rings and hydroxyl groups distinguish the various classes within the group. Chalcones, flavones, flavanones, flavonols, anthocyanins, and isoflavones are some of them. (Williams and Grayer, 2004). In a wide range of nutraceutical, pharmacological, therapeutic, and cosmetic applications, flavonoids are now considered as an essential component. This is attributed by their ability to influence important cellular enzyme function in addition to having anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic effects.

Quercetin, a flavonoid found in many plants, has antioxidant property. It is presently popular at health food stores, even though any benefits are not proven (Graefe *et al.,* 1999). Silybin, one of the silymarins, a mixture of several flavanone derivatives (flavonolignans), is found in the fruit of the milk thistle (*Silybum marianum*). It is used to cure numerous liver disorders (Sridar *et al.,* 2004). Flavonoids serve as special UV filters, signal molecules, phytoalexins, allopathic substances, detoxifying agents, and antimicrobial defensive compounds. They also protect plants from a variety of biotic and abiotic stresses. (Takahashi A & Ohnishi T, 2004; Panche *et al.,* 2016).

Phenolic acids

Phenolic acids contain one carboxylic acid functional group. The hydroxycinnamic and hydroxybenzoic structures are the two distinctive carbon frameworks present in naturally occurring phenolic acids. Hydroxycinnamic acid compounds are synthesized as simple esters with glucose/hydroxycarboxylic acids. Two metabolic pathways are involved in the synthesis of phenolic compounds: the shikimic acid pathway where, phenylpropanoids are majorly formed and the acetic acid pathway, in which simple phenol are the main products. A majority of phenolic compounds in plants are synthesized via, the phenylpropanoid pathway (Hollman, 2001). The phenolic acids in plants have diverse function including a role in nutrient uptake, structural components, protein synthesis, enzyme activity, photosynthesis, and also in allelopathy (Lyu, 1990). The main polyphenols synthesized by plants are phenolic acids, which have a variety of biol ogical uses and serve as the ancestor of bioactive compounds frequently employed in the fo

od, cosmetics, and pharmaceutical industries (Croft, 1998). In pharmaceutical industries they are used as antioxidant, antidiabetic agent and antimicrobial agents (Kumar & Goel 2019).

Saponins

Saponins are class of secondary plant metabolites. They are capable of forming soap-like, stable foam in aqueous solutions. Glycosylated steroids, steroid alkaloids and triterpenoids compounds are included in the saponins. Spirostan and furostan derivatives are the two most common forms of steroid aglycones. One or more sugar moieties with glucose, galactose, arabinose, xylose, rhamnose, or glucuronic acid glycosidically linked to a sapogenin (aglycone) make up the carbohydrate component. Monodesmoside saponins are those that have a single sugar molecule attached at the C-3 position, and bidesmoside saponins are those that contain at least two sugars, one attached to the C-3 and one at the C-22 positions (Lasztity R, Hidvegi M, Bata A 1998). Their anti-inflammatory, anticancer and anti-diabetic etc. properties made them as a potential drug however they are poorly absorbed.

Terpenoids

Terpenoids, also referred as isoprenoids, are the most abundant and structurally diverse natural compounds. The "terpene" generic name was originally applied to the hydrocarbons present in turpentine, the suffix "ene" representing the presence of olefinic bounds (Ludwiczuk *et al.,* 2017). Terpenoids are derived from isoprene units which contains five-carbon. The majority of terpenoids are multicyclic compounds with distinct functional groups and basic carbon skeletons (Elbein AD, Molyneux RJ, 1999). Terpenes are abundant in nature and are majorly found in plants as the constituents of essential oils. Their building block is the hydrocarbon isoprene, CH2=C(CH3)- CH=CH2. Terpene hydrocarbons have molecular formula (C5H8) n (Rex *et al.,* 2018). Terpenoids are classified depending upon the number and structural organization of carbons formed by the linear arrangement of isoprene units. It is followed by cyclization and rearrangements of the carbon skeleton with an empirical feature known as the isoprene rule (Zwenger and Basu, 2008). The different classes of terpenoids includes Hemiterpenoids, Monoterpenoids, Sesquiterpenoids, Diterpenoids, Sesterterpenoids, Triterpenoids, Tetraterpenoids (carotenoids), and Polyterpenoids.

Among terpenoids isomerism is common, and the pairs of the isomeric forms can be isolated from plants. The terpenoids shows antimicrobial, analgesic, antioxidant, anti-

inflammatory, antispasmodic, anti-inflammatory and immunostimulant properties (Bruneton, 1999).

Name	No. of Isoprene Units	No. of Carbon Atoms	General Formula
Hemiterpenoids	1	5	C_5H_8
Monoterpenoids	2	10	C10H16
Sesquiterpenoids	3	15	C15H24
Diterpenoids	4	20	C20H32
Sesterterpenoids	5	25	C25H40
Triterpenoids	6	30	C30H48
Tetraterpenoids	8	40	C40H64
Polyterpenoids	>8	>40	(C5H8)n

Phytosteroids

Phytosteroids are plant steroids that may or may not act as weak hormones in the body. Plant steroids also have a fundamental ring structure in common with animal steroids, however due to distinct chemical groups connected to the primary ring in different places, they are not equivalent to animal steroids. (Ngoci, *et al.,* 2011). All the plant steroids are hydroxylated at C-3 and are, actually, sterols. The role of the phytosterols is not well understood. There is evidence that certain of the phytosterols are effective against cardiovascular diseases (Kris-Etherton *et al.,* 2002). They are mostly used to cure reproductive issues, such as the treatment of venereal diseases, to ensure an easy delivery they are used during pregnancy, and to encourage fertility in women and libido in men. They also act as sex hormones derivatives for instance, and can be metabolized to either androgen or estrogen-like substances, therefore they are potential source of contraceptives (Edeoga *et al.,* 2005; Ngoci *et al.,* 2011). They are also used as anti-microbial, analgesic, anti-inflammatory agents, in treating stomach ailments and in decreasing serum cholesterol levels (Ngoci, *et al.,* 2011).

Fatty acids

Fatty acids are the simplest lipids. They can be identified by their long hydrophobic tail and polar hydrophilic head region. Some lipids, such as the fats, are used to store energy, the majority are used to form lipoprotein membranes. Although there are well over one hundred different kinds of fatty acids, oleic acid and palmitic acid are the most

prevalent in plants. Evidently, linolenic acid is a major nutrient for cardioprotection (De Lorgeril and Salen, 2004).

Tannins

Tannins are rich in phenolic groups, water-soluble oligomers and have the ability to bind or precipitate water soluble proteins (Hagerman and Butler, 1989). They are commonly occurred in vascular plants, found primarily in the woody tissues and can also be present in leaves, flowers, or seeds. Plant tissues which are rich in tannin content have a very bitter taste and are avoided by most feeders. Condensed tannins or hydrolyzable tannins are the two groups of tannins. Condensed tannins are synthesized by the condensation of flavanols to form polymeric networks. Proanthocyanidins are example of condensed tannins. Hydrolyzable tannins are esters of a sugar frequently glucose with one or more trihydroxybenzenecarboxylic acids for instance gallic acid. With albumin, starch, or gelatin these materials give insoluble precipitates. The mode of action of tannins permits the binding of proteins (adhesins), hinders enzyme-substrate deprivation, form complexes with cell wall, increases intestinal mucosa resistance and decreases secretion, increases the supply of animal digestible proteins by forming protein complexes in the rumen, and slows down digestive-tract metabolism (Cowan, 1999; Tiwari *et al.,* 2011).

Hydrocarbons

They comprise a relatively small group of compounds. They are the least polar organic natural products, contain only hydrogen and carbon atoms. The aliphatic hydrocarbons are straight chain and generally have odd number of carbon atoms, which results from the decarboxylation of their fatty acid counterparts (Savage *et al.,* 1996). These compounds have comparatively simple structures. Hydrocarbons, may be either saturated or unsaturated. Each double bond results in two fewer hydrogen atoms relative to the saturated counterpart. They may have straight chains, branched chains, and also rings. As they are purely organic in nature, they are extremely insoluble in water, and are "greasy." (Brielmann *et al.,* 2006).

Glycosides

Glycosides are compounds comprising a carbohydrate residue in the same molecule. In them, the carbohydrate residue is attached by an acetal linkage of C – 1 to the non – carbohydrate residue I,e. aglycone. The steroid as aglycone component in combination with sugar molecules is frequently found. They are vital in medicine owing to their action on heart and are used in cardiac insufficiency [Balch and Balch, 2000]. Therefore, cardiac

glycosides can be used in the management of congestive heart failure and cardiac arrhythmia as drugs.

Conclusion:

Phytochemicals account for several pharmacological properties. Plants contain compounds such as flavonoids, alkaloids, and tannins that have these life-saving therapeutic activities. Some of important plants which could be a great source of biologically important novel phytoconstituents are on the verge of extinction due to their unsustainable use, destruction of forests, and habitat destruction. In order to prevent this the sustainable use of these plant should be closely monitored. To maximize the health benefits of these bioactive substances, peoples should be educated on how to use phytochemicals properly.

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