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Triterpenoids: A review

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Abstract
Ayurveda is a traditional system of medicine in which herbal therapies were used systematically. Plants have been used for medicinal purposes long before prehistoric period. Ayurveda, the traditional system of medicine continue to be widely practiced on many accounts. There is an unprecedented growing interest in natural triterpenes in the last few decades due to the discovery of their potential biological and pharmacological activities. Plant terpenoids are used extensively for their aromatic qualities. They play a role in traditional herbal remedies and are under investigation for anti bacterial, anti neoplastics, and other pharmaceutical functions. Triterpenoids possess a rich chemistry and pharmacology with several pentacyclic motifs. Triterpenoids isolated and characterized from various sources are reviewed. The biological activities and health benefits of the triterpenoids are also discussed.

Keywords: triterpenoids, isoprenoids, terpenoids, pharmacological activities, pentacyclic triterpenoids

Introduction

The terpenoids sometimes called isoprenoids, are a large and diverse class of naturally occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways. Most are multicyclic structures that differ from one another not only in functional groups but also in their basic carbon skeletons. These lipids can be found in all classes of living things, and are the largest group of natural products. About 60% of known natural products are terpenoids [1].

Terpenoids are hydrocarbons are obtained from oxygenated, hydrogenated and dehydrogenated derivatives. Triterpenes are hydrocarbons and possess no heteroatoms; functionalized triterpenes should instead be called triterpenoids. However this distinction is not always adhered to in scientific literature, with the two terms triterpene and triterpenoid often being used interchangeably. Triterpenoids possess a rich chemistry and pharmacology (e.g. cholesterol) with several pentacyclic motifs. Lupane, oleanane and ursane show particular promise as anti-cancer agents. Triterpenoids, which extract from Sympcocos Racenosa, are a group of Terpenes (isoprenoids) is defined as terpenoid derviatives of triterpene molecules, including Oleanolic acid found in honey mesquite, garlic, java apple, etc.; Ursolic acid – apples, basil, bilberries, cranberries, elder flower, peppermint, lavender, etc., moronic acid – Rhus javanica, mistletoe, etc. and Betulinic acid found in the bark of several species of plants such as birch. Sympcocos Racenosa is the dominant tree which use to extract triterpenoids. Plant terpenoids are used extensively for their aromatic qualities and play a role in traditional herbal remedies [2, 3].

Triterpenes are a class of chemical compounds composed of three terpene units with the molecular formula $C_{30}H_{48}$; they may also be thought of as consisting of six isoprene units. Animals, plants and fungi all create triterpenes, with arguably the most important example being squalene as it forms the basis of almost all steroids. Triterpenes exist in a huge variety of structures with nearly 200 different skeletons known from natural sources or enzymatic reactions. These may be broadly divided according to the number of rings present; although in general pentacyclic structures (5 rings) tend to dominate. By definition triterpenes are hydrocarbons and possess no heteroatoms; functionalized triterpenes should instead be called triterpenoids. However this distinction is not always adhered to in scientific literature, with the two terms triterpene and triterpenoid often being used interchangeably. Triterpenoids possess a rich chemistry and pharmacology [4].

Traditional medicine has been a fertile source for revealing novel lead molecules for modern drug discovery. In plants, terpenoids represent a chemical defense against environmental stress and provide a repair mechanism for wounds and injuries. Interestingly, effective ingredients in several plant-derived medicinal extracts are also terpenoid compounds of monoterpenoid, sesquiterpenoid, diterpenoid and carotenoid groups. Inflammatory diseases and cancer are typical therapeutic indications of traditional medicines1. According to WHO, herbal medicines serve the health needs of about 80% of the world's population, especially for millions of people in the vast areas of developing countries [5].

There are many different classes of naturally occurring compounds. Terpenoids also form a group of naturally occurring compounds majority of which occur in plants, a few of them have also been obtained from other sources. Terpenoids are volatile substances which give plants and flowers their fragrance. They occur widely in the leaves and fruits of higher plants, conifers, citrus and eucalyptus. The term 'terpene' was given to the compounds isolated from terpentine, a volatile liquid isolated from pine trees. The simpler mono and sesquiterpene is chief constituent of the essential oils obtained from sap and tissues of certain plant and trees. The di and tri terpenoids are not steam volatile.

They are obtained from plant and tree gums and resins. Tertraterpenoids form a separate group of compounds called 'Carotenoids'. The term 'terpene' was originally employed to describe a mixture of isomeric hydrocarbons of the molecular formula $C_{10}H_{16}$ occurring in the essential oils obtained from sap and tissue of plants, and trees. But there is a tendency to use more general term 'terpenoids' which include hydrocarbons and their oxygenated derivatives. However the term terpene is being used these days by some authors to represent terpenoids [6, 7, 8, 9, 10, 11].

Triterpenes are widely distributed in the plant and marine animal kingdoms, where they occur either in the free state, as esters, or as glycosides (saponins). They are composed of six isoprene units $(C_5H_8)_6$ from mevanolic acid or deoxyxylulose phosphate, and are derived from the reductive coupling of two molecules of farnesyl pyrophosphate by squalene synthase. Triterpenoids are usually classified into three groups: acyclic, tetracyclic and pentacyclic [12, 13].

Secondary metabolites are natural products that often have an ecological role in regulating the interactions between plants and their environment. They can be defensive substances such as phytoalexins and phytoanticipins, antifeedants, attractants, and pheromones [14]. The importance of plant secondary metabolites in medicine, agriculture and industry has led to numerous studies on the synthesis, biosynthesis and biological activity of these substances. It has been estimated that over 40% of medicines have their origins in these active natural products [15]. A prominent group of natural products is the terpenes and their derivatives [16, 17].

Cancers

In a study of "Pentacyclic Triterpenes of the Lupane, Oleanane and Ursane Group as Tools in Cancer Therapy" by Melanie N. Laszczyk, © Georg Thieme Verlag KG Stuttgart • New York, posted in Thieme Ejoiurnals, researchers found in abstract that Triterpene acids as well as triterpene monoalcohols and diols also show an antioxidative potential. The pharmacological potential of triterpenes of the lupane, oleanane or ursane type for cancer treatment seems high; although up to now no clinical trial has been published using these triterpenes in cancer therapy. They provide a multitarget potential for coping with new cancer strategies. Whether this is an effective approach for cancer treatment has to be proven. Because various triterpenes are an increasingly promising group of plant metabolites, the utilisation of different plants as their sources is of interest. Parts of plants, for example birch bark, rosemary leaves, apple peel and mistletoe shoots are rich in triterpenes and provide different triterpene compositions.

Colon Cancer

According to the study of" Triterpenes from Ganoderma Lucidum induce autophagy in colon cancer through the inhibition of p38 mitogen-activated kinase (p38 MAPK)" by Thyagarajan A, Jedinak A, Nguyen H, Terry C, Baldridge LA, Jiang J, Sliva D. (Source from Methodist Research Institute, Indianapolis, Indiana, USA), posted in PubMed, researchers indicated in abstract that autophagy is mediated through the inhibition of p38 mitogen-activated protein kinase (p38 MAPK) because p38 MAPK inhibitor, SB202190, induces autophagy and expression of Beclin-1 (1.2-fold increase) and LC-3 (7.4-fold increase), and GLT suppresses phosphorylation of p38 MAPK (approximately 60% inhibition) in colon cancer cells. Taken together, our data demonstrate a novel mechanism responsible for the inhibition of colon cancer cells by G. lucidum and suggest GLT as natural product for the treatment of colon cancer.

Inflammatory Response

In a study of " Suppression of the inflammatory response by triterpenes isolated from the mushroom Ganoderma lucidum" by Dudhgaonkar S, Thyagarajan A, Sliva D. (Source Cancer Research Laboratory, Methodist Research Institute, 1800 N Capitol Ave, E504, Indianapolis, IN 46202, USA), posted in PubMed, researchers found that Apart from its anti-inflammatory activity, GLT suppressed cell proliferation of RAW264.7 cells through cell cycle arrest at G0/G1-G2M, which was mediated by the down-regulation of expression of cell cycle regulatory proteins cyclin D1, CDK4 and cyclin B1, respectively. In conclusion, the anti-inflammatory and anti-proliferative effects of GLT on macrophages are mediated through the inhibition of NF-kappaB and AP-1 signaling pathways.

Hepatoprotective

According to the study of " Hepatoprotective constituents of Torilis radiata Moench (Apiaceae) by Ezzat SM, Abdallah HM, Fawzy GA, El-Maraghy SA (Source from a Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt), posted in PubMed, researchers found that The hepatoprotection of the AE and its fractions was assessed in terms of the reduction in histological damage, accompanied by restoration of the liver enzymes (alanine amino transferase (ALT), aspartate amino transferase (AST), lactate dehydrogenase (LDH)), a reduction in the inflammatory markers (tumour necrosis-α (TNF-α), nitric oxide (NO), N-acetyl-β-D-glucosaminidase (NAG) and myloperoxidase (MPO) in serum) and restoration of the oxidant balance by decreasing the serum and hepatic malondialdehyde (MDA) levels, along with increasing the activity of hepatic catalase (CAT), glutathione peroxidase (GSHPx) and the non-enzymatic antioxidant glutathione (GSH).

Breast Cancer

According to teh study of" Inhibition of Wnt signaling by cucurbitacin B in breast cancer cells: Reduction of Wnt associated proteins and reduced translocation of galectin-3-mediated β-catenin to the nucleus" byDakeng S, Duangmano S, Jiratchariyakul W, U-Pratya Y, Bögler O, Patmasiriwat P. (Source from Faculty of Medical Technology, Mahidol University, Bangkok, Thailand; Department of Neurosurgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX. Biochem.© 2011 Wiley-Liss, Inc.), posted in PubMed, researchers indicated in abstract that The relative luciferase activity was reduced when we treated cells with cucurbitacin (tetracyclic triterpenes) B compound for 24 hours. Our data suggest that cucurbitacin B may in part induce apoptosis and exert growth inhibitory effect via interruption the Wnt signaling. J. Cell.

Human Immunodeficiency Virus (HIV)

In a study of "Celastrol inhibits Tat-mediated human

immunodeficiency virus (HIV) transcription and replication" by Narayan V, Ravindra KC, Chiaro C, Cary D, Aggarwal BB, Henderson AJ, Prabhu KS. (Source from Center for Molecular Immunology and Infectious Disease and Center for Molecular Toxicology and Carcinogenesis, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, PA 16802, USA.) posted in PubMed, researchers found that Celastrol (Cel), a triterpenoid MAE isolated from Tripterygium wilfordii, exhibited the highest inhibitory activity against Tat. Using biochemical techniques, we demonstrate that Cel, by covalently modifying the cysteine thiols, inhibits Tat transactivation function. Using circular dichroism spectroscopy, we show that alkylation of Tat brought about a change in the secondary structure of Tat, which inhibited the transcription elongation of the HIV proviral genome by effecting mechanisms other than Tat-TAR (transactivation-responsive region) interaction. Our results demonstrate the underlying mechanism of antiretroviral activity of the plant-derived MAEs and suggest that Cel could serve as a lead compound to develop novel antiviral therapeutics.

Antioxidant Activities

According to the result of" Phytochemical screening, antioxidant, and antimicrobial activities of the crude leaves' extract from Ipomoea batatas (L.) Lam? by Pochapski MT, Fosquiera EC, Esmerino LA, Dos Santos EB, Farago PV, Santos FA, Groppo FC. (Source from Department of Pharmacology, Anesthesiology and Therapeutics, Piracicaba Dental School, University of Campinas, Piracicaba, SP, Brazil) posted in PubMed, researchers indicated that triterpenes/steroids, alkaloids, anthraquinones, coumarins, flavonoids, saponins, tannins, and phenolic acids. Total contents of 345.65, 328.44, and 662.02 mg were respectively obtained for alkaloids, anthraquinones, and phenolic compounds in 100 g of the dry sample. The total antioxidant capacity was 42.94% as compared to ascorbic acid. For antimicrobial studies, no concentration of the SP freeze dried extract was able to inhibit the growth of Streptococcus mutans, S. mitis, Staphylococcus aureus, and Candida albicans in both agar disk and agar well diffusion tests.

Oral mucosa cancer

According to the result of the study "Study of the extraction process and in vivo inhibitory effect of ganoderma triterpenes in oral mucosa cancer" by Gao Y, Zhang R, Zhang J, Gao S, Gao W, Zhang H, Wang H, Han B. (Source from Stomatology Hospital, Jilin University, Changchun 130021, Jilin, China), posted in PubMed, researchers indicated that Using the optimized extraction process, ganoderma triterpenes could be extracted with high efficiency, and the results of animal tests showed inhibitory effects of ganoderma triterpenes on oral mucosa cancer.

Anti bacterial activity

In a study of "Jacaranda cuspidifolia Mart. (Bignoniaceae) as Antibacterial Agent" by Arruda AL, Vieira CJ, Sousa DG, Oliveira RF, Castilho RO. (Source from Course of Pharmacy, Department of Biological Sciences and Health, Dom Bosco Catholic University, Campo Grande, Mato Grosso do Sul, Brazil), researchers found that Phytochemical analysis of JCME and JCCF gave positive results for saponins, coumarins, flavonoids, tannins, quinones, alkaloids, triterpenes, and steroids. Verbascoside was isolated and identified as a major peak in JCME and JCCF high-performance liquid chromatography fingerprints and might contribute to the observed antimicrobial activity.

Human T-cell leukemia

According to the study of " Apoptosis induction through proteasome inhibitory activity of cucurbitacin D in human T-cell leukemia" by Ding N, Yamashita U, Matsuoka H, Sugiura T, Tsukada J, Noguchi J, Yoshida Y. (Source from Department of Immunology and Parasitology, School of Medicine, University of Occupational and Environmental Health, Japan), posted in PubMed, researchers found in abstract that cucurbitacin D was found to inhibit proliferation and to induce apoptosis of T-cell leukemia cells,… Cucurbitacin (tetracyclic triterpenoid) D induced apoptosis through suppression of proteasome activity both in vitro and in vivo, making cucurbitacin D a promising candidate for clinical applications in the treatment of T-cell leukemia.

Analgesic and Anti-Nociceptive

In a study of "Analgesic and anti-nociceptive activity of hydroethanolic extract of Drymaria cordata Willd" by Barua CC, Roy JD, Buragohain B, Barua AG, Borah P, Lahkar M. (Source from Department of Pharmacology and Toxicology, College of Veterinary Science, Assam Agricultural University, Khanapara, Assam, India), posted in PubMed, researchers concluded that DCHE was effective in both non-narcotic and narcotic models of nociception, suggesting its possible action via peripheral and central mechanism. It also abolished the early phase in formalin-induced paw licking model, suggesting complete inactivation of C-fiber at higher dose. The activity can be attributed to the phyto-constituents viz tannins, diterpenes, triterpenes and steroids present in the DCHE extract. In conclusion, DCHE (Drymaria cordata hydroethanolic extract) can be developed as a potent analgesic and anti-nociceptive agent in future.

Anxiolytic

According to the result of a study of "Anxiolytic effect of hydroethanolic extract of Drymaria cordata L Willd" by Barua CC, Roy JD, Buragohain B, Barua AG, Borah P, Lahkar M. (Source from Department of Pharmacology & Toxicology, College of Veterinary Science, AAU, Khanapara, Guwahati 781 022, India.), posted in PubMed, researchers found that Similarly, in elevated plus maze test, there was significant increase in the time spent and number of entries in open arm as compared to the time spent and number of entries in closed arm in dose dependent manner. In light/dark exploration test, another model for anxiolytic activity, the time spent in lit box, number of crossing and the latency period increased significantly with reduction in time spent in dark box after treatment with DCHE. The presence of phytochemicals viz. triterpenes, diterpenes, steroids and tannins might contributeto its anxiolytic activity.

Biologically active triterpenoids

A diet rich in fruits and vegetables has been identified to

confer multiple health benefits, including the reduction of cardiovascular disease risk. Fruits like apple, grape berry, olive, tomato, and mango all contain triterpenoid compounds with cardio-protective and antioxidant activities that can significantly attenuate or delay cardiovascular disease onset. Various clinical trials have been conducted on humans assessing the potential role of triterpenoid usage in the prevention of such chronic disorders, and the possible mechanisms responsible for the observed therapeutic actions.

Main sources of some triterpenoids

Skin of the fruits

The surface tissue of fruits is not only the first line of communication system for the surrounding biotic and abiotic environment, but a protective barrier against water loss, chemical or biological attack, mechanical injuries, and microbial infection. Most of the compounds are found in the peel of the fruit, especially within the cuticle [18, 19].

Tomato Triterpenoids

Over the last century, tomato (*Solanum lycopersicum* L. or *Lycopersicon esculentum* L.) has gained great popularity by the general public and the scientific community for their potential health benefits. Being cultivated globally both indoors and outdoors, it is a fruit that has been studied extensively. In terms of their triterpenoid content, research has especially focused on the cuticular waxes of the tomato fruit more than most other fruits. The main cutin monomers of the tomato fruit cuticle include 16-hydroxyhexadecanoic acid [20, 21].

Ursane Triterpenes

C29 hydrocarbon n-nonacosane is one of the major n-alkanes compounds in the cuticle of apples. The cutin of the apple membrane is found in the cuticle, and it constitutes over 50-60% of the weight of the overall apple [22].

Apple peel triterpenes

Apples compose a significant portion of the human diet, with a massive global production of approximately 62 million tonnes per year. Earlier studies have explored the effectiveness of apple on its cardioprotective properties. Different tissue types individually containing phytochemicals in different compositions compose apple fruits, such as the peel, cortex, core, and seed. Many different compounds have been identified in the apple peel such as: organic acids, phenolic acids, flavonoids, coumaryl fatty acid esters, sesquiterpenes, and triterpene acids. Triterpene acids are documented to confer a number of potential health benefits. Methods using the ultra-performance liquid chromatography-electrospray ionization MS analysis determined that fruit peels, pomace, flesh, and juice are a good source of high levels of bioactive triterpenes, with the peel being the richest source. As well, triterpenoids isolated from apple peel had demonstrated more potent antioxidative and antiproliferative activity, when compared to the apple flesh [23, 24].

Oleane Triterpenes

Oleanolic acid (OA), maslinic acid (MA), and β-amyrin are all part of the oleanane triterpene family. These compounds can be found in the peel of grapes, olives, and tomatoes, respectively. As are found to be isolated from over 1620 plant species, and they can be used for chemical modification as they have the capacity to act as starter molecules. This can improve the natural bioavailability of grapes by producing more effective compounds through the modification on the C-3 hydroxyl, the C-12 C-13 double bond, and the C-28 carboxylic acid, thus contributing to the fruit's overall anti-oxidant, anti-inflammatory, and cardiovascular activities [18].

Olive Triterpenes

Vast interest has previously been devoted to characterizing the ways in which pentacyclic triterpenoids in olives mediate health and disease prevention. Various properties that may be useful in modulating cardioprotection activity, anti-inflammatory activity, and antioxidant protection have previously been identified upon the consumption of the olive fruit. For instance, cell oxidative damage is related to multiple diseases that could be prevented through the antioxidant properties of olive oil triterpenes. Triterpenic acids present in olive fruits are bioactive compounds that may exhibit multiple nutraceutical activities. The main triterpenes found in olives, olive tree leaves, and virgin olive oil are oleanolic acid, uvaol, erythrodiol, and maslinic acid. The concentration of these triterpenes depends on the quality of the olive, the type of the tree, and the degree of ripeness [25, 26].

Mango Lupane Triterpenes

Many triterpenoids are known for exhibiting similar significant pharmacological properties; lupeol for example is known to have properties that significantly influence anti-inflammatory activities. Lupeol (Lupa-21, 20(29) dien 3 beta-ol) is a naturally occurring pentacyclic triterpene (also known as Fagarsterol) under the lupane triterpene family, predominantly present in mango. As there has been limited number of studies conducted that focused on the effect of lupane triterpene compounds on health, this section will focus on the triterpenoid composition of mango fruits and their effects on CVD and inflammation.

Mango (*Mangifera indica L.*) is a fruit consumed worldwide, being one of the most commonly consumed fruits in the tropical countries. Having been part of the indigenous medical systems for over 4000 years, mango fruits have been considered a good source of bioactive compounds that can be used towards preventing diseases and promoting overall good health in humans [27, 28, 29].

Conclusion

From several *in-vivo, in-vitro*, and human studies, it has been demonstrated that many triterpenoid compounds present in fruits and vegetables possess potent and desirable biological activities that can protect against cardiovascular disease and inflammation etc. This knowledge about the medicinal plants usage can also be extended to other fields like field of pharmacology. A large scale isolation and further spectral techniques are required to isolate and identify a particular compound responsible for pharmacological action.

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Conflict of interest

There is no conflict of interest.

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