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RESEARCH ARTICLE

Ellagitannins and Their Metabolites: Advances in Classification, Metabolic Pathways, and Health Benefits For Animals And Humans

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Abstract: *Background:* Ellagitannins (ETs) are a class of bioactive hydrolyzable tannins found in various fruits, nuts, and medicinal plants. Following ingestion, they are metabolized into urolithins by the gut microbiota, yielding compounds with significant biological activity.*Purpose:* This review comprehensively examines the health-promoting potential of ETs and their metabolites, focusing on their antioxidant, anti-inflammatory, and anti-cancer properties, and their application in managing chronic diseases.*Methods:* A systematic assessment of the current literature was conducted to elucidate the taxonomy, biosynthesis, metabolic pathways, and multifaceted bioactivities of ETs, with special attention to their role in functional foods and nutraceuticals.*Results:* ETs and their gut-derived metabolites, such as urolithin A, demonstrate efficacy in alleviating oxidative stress, reducing inflammation, and inhibiting cancer cell proliferation. These actions contribute to potential benefits for cardiovascular, metabolic, and neurological health. Furthermore, preliminary studies in animal husbandry suggest they can enhance growth and immune function. However, limitations such as low bioavailability and instability during processing restrict their broader application.
Conclusion: Ellagitannins present a promising avenue for the development of natural therapeutics and functional ingredients. Future research should prioritize overcoming bioavailability challenges and conducting large-scale human clinical trials to validate their health benefits and establish definitive dietary and pharmaceutical guidelines.

Keywords:Gut microbiota, urolithins, Antioxidants, ellagitannins, and functional foods

INTRODUCTION

INTRODUCTION TO ELLAGITANNINS

One rare kind of tannins that can be hydrolyzed known as ellagtannins are types of esters consisting of hexahydroxy diphenic acid (HHDP) together with a common triglyceride which is often beta-D-glucose. They are proven by their byzantine molecular designs. They come in multiple forms when these substances are analyzed: C-glycosidic (such as vescalagin & castalagin), oligomeric (such as nupharin E, nupharin C, & hirtellin A), and monomeric (such as nupharin A, geraniin, & tellimagrandin II). The carbon-oxygen-carbon bonds that connect the monomeric units frequently lead to the formation of large molecules, for instance, dimers and oligomers [1]. The intricate organization of ellagitannins plays a role in both their biological activities and hydrolysis. They get hydrolyzed in the guts still two days later they release ellagic acid even though they are resistant to the stomach acid. Consequently, the intestinal bacteria modify this acid into viable compounds such as urolithins A and B [2,3]. Ellagitannins are a type of the ones that naturally exist in many fruits, nuts, seeds, and plants. Some of them such as raspberries have a lot of ellagitannins. Raspberries being an example of ellagitannin-rich fruits. The two primary ellagitannins noted in raspberries besides lambertianin C is sanguiin H-6, that exists between 2.63 to 3.30 mg/g [4,5]. Basically, all the fruits contain ellagtannins, but adventurous pomegranates, cloudberries, tamed blackberries, and strawberries have the highest significance in them. Blackberries are rich with sanguiin H-6 (1.50-2.00 mg/g), and strawberries are rich in agrimoniin (0.77-0.85 mg/g) as well as sanguiin H-6 (0.25 mg/g) being its main component. Pomegranates have a basic content of punicalagin (0.35-0.75 mg/g), cloudberries, in their turn, are famous for the whole range of antioxidants that are found in these berries, among others, lambertianin C (0.56-3.60 mg per gram) and

sanguiin H-6 (3.15 mg/g). Raspberries play an important role in the positive effects of these biologically active compounds that nature provides, and these compounds are associated to the healing properties of antioxidants along with those of diets that contain ellagitannins. [6-8] There is a substantial volume of those substances in walnuts, pecans, as well as chestnuts; however, they are quite common in other nuts, liqueurs, and herbal remedies as well. Pecans have significantly greater quantities of pedunculagin, their levels are fluctuating between 20.96 and 86.20 mg/g, while walnuts contain an average of 16.04 mg/g. Chestnuts, on the other hand, have less castalagin, from 0.16 to 2.49 mg / 100 grams [9,10]. Pomegranate juice including punicalagin at approximately 1500–1900 mg/L level ranks ellagitannins first, along with nuts. Moreover, they are inclusive in beverages like whiskey namely whose vescalagin levels may even be as high as 1 to 2 mg/L or red wine which happens to be aged within oak barrels, so it contains vescalagin at a level around 9.4 mg/L [11,12]. Moreover, there is the advantage of using culinary herbs and medicinal plants for health, for instance, Punica granatum, Camellia sinensis, and Agrimonia spp. which are a myriad of them containing ellagitannins [13]. Long utilized for their health benefits, ellagitannins are good examples of these plants. For instance, they can be cited as inhibitory in relation to their anti-cancer action, anti-inflammatory, and antibacterial and antioxidant functions. Research of the prevention of continuous diseases such as cancer, neurological disorders, and cardiovascular diseases have been conducted, as well as those of the possible relevance of ellagitannins have been initiated. The potent antioxidant properties are a main characteristic of ellagitannins. These powerful natural ellagitannins possess properties that inhibit free radicals and thus reduce oxidative stress, which can lead to the development of tumors and damage the walls of arteries [14]. They all are highly effective against all kinds of bacteria. Indeed, they have been indicated as working well against several pathogens such as viruses, fungi, and bacteria. The effectiveness against bacteria that are not affected by antibiotics, such as methicillin-resistant Staphylococcus aureus (MRSA) has also been observed, suggesting the use of this natural product to substitute antibiotic resistant strains [15]. However, the fact that they also have antibacterial activity is the feature that makes them widely successful against both chronic and infectious diseases. Very common members of the family are ellagitannins and the example that will be measured here is ellagic acid. They accomplish the anti-inflammatory effect by modulating the level of cytokines. The proinflammatory cytokine IL-6 is likely to be downregulated and so is the anti-inflammatory.

cytokine IL-10 likely to be upregulated. These compounds can be utilized for their antiinflammatory effects as well. Their capacity of regulating inflammatory reactions is clearly demonstrated by their use in pharmacotherapy. Besides, they have potential use in treating inflammation-driven diseases and improving immune function [16,17]. As well, ellagitannins have potential antitumor qualities by preventing the growth of cancer cells via several methods, such as apoptosis induction and carcinogenesis prevention. They have been effective against a variety of malignancies, including colorectal, lung, female breast, liver, and esophageal tumors [18]. The complex structure of ellagitannins prevents them from being fully absorbed in the stomach, but in the intestines, they hydrolyze and generate ellagic acid. The gut bacteria then breaks down this chemical to produce beneficial compounds called urolithins, such as urolithin both A and B. These metabolites subsequently enter the liver for circulation after being absorbed into the bloodstream, where they start to have biological effects. The transformation procedure shows how important gut microbiota is for improving ellagitannins' bioavailability and therapeutic effectiveness [19,20]. One important derivative of ellagitannins is ellagic acid, which may be digested in the stomach and subsequently transformed by dimethylated ellagic acid lactic acid. The gut microbiota urolithins make, which are the main bioactive metabolites of ellagitannins. Urolithins, especially urolithin A and B, are like hormones as well as serve as the major agents in the immunity linked to ellagitannins [21,22]. Ellagitannins can perform a variety of biological activities, for example anticancer, anti-inflammatory, and antibacterial effects. They are very efficient in destroying bacteria families including, for instance, bacteria, fungi, and viruses. They can be used with special effectiveness by bacteria strains such as Acinetobacter baumannii which resist the effect of antibiotics, for example, MRSA and carbapenem-resistant Acinetobacter. These, furthermore, through inhibiting the production of cytokines and engaging the synthesis of pro-inflammatory substances, such as prostaglandin E2 (PGE2) and nitric oxide (NO), enhance the alleviation of inflammation [15,23]. Ellagitannins are also effective in preventing the occurrence and growth of cancer by means of apoptosis and by increasing the generation of free radicals, which damage the cancer cells and, hence, stop cancer growth. They have proven to be active in numerous cancer types, like the ones that develop in breast, liver, colon, esophagus, and lung [18]. Such substances are usually

produced only by pharmaceutical and nutraceutical companies because of their large health benefits. Among the existing commercial products available are Ellagic Acids New Once again, whose promotions emphasize skincare, and VitaPurity Ellagic Ultra, a nutritional supplement that contains ellagic acid. Also, pomegranate extract, which is known for its strong antiinflammatory and antioxidant activities, and is very rich in ellagitannins, are in great demand all over the world [24,25].

CLASSIFICATION OF ELLAGITANNINS

Ellagtannins differ from hydrolyzable tannins in having a glucose core with several HHDP (hexahydroxydiphenoyl) moieties attached. They are also bettyer (sic) at math. The structural complexity of these molecules further subdivides them into other groups, with the monomeric ellagitannins being kept at the simplest stage [26, 27]. Tellimagrandin I, II, pedunculagin, and casuarictin are examples of monomeric ellagitannins which have HHDP units that have been esterified with a glucose molecule. These substances are the basic units that ellagitannins are built on, and then they may go through several other processes such as C-C couplings, oxidation, and more esterification to create a lot of different changes within this class of natural substances [28, 29]. C-Glycosidic ellagitannins are a special class of polyphenolic chemicals that differ from the more common O-glycosidic ellagitannins due to their C-glucosidic bond. In this class are the chemicals castalagin-type and casuarinin-type that one may choose from [30, 31]. Oak, wood, and wine, some of the most well-known substances being castalagin as well as vescalagin that usually help astringent features and aging potential are included in the castalagin-type [32]. However, castalagin-type such as substances like casuarinin along with **s**tachyurin, which can also be found in plants of the genus Casuarina as well as Stachyurus, are included in the casuarinin-type [33, 34]. Tannins are complex plant compounds with a unique carbon-carbon compact structure, in which a C-glycosidic one is combined with the flavan-3-ol units like epicatechin or catechin. Ones such as acutissimin A or guajavin B are the compounds arising from this underlying structure having bioactivity nature exhibited [35]. When monomer units are polymerized by the formation of between-molecular C-O or C-C bonds, polyphenolic substances of the class of oligomeric ellagitannins are invented. The fact is that they are chemically different due to the following features: their functional groups, ring size, and the presence of valoneoyl units in their structures. There are two types of hydrolyzable tannins. The first consists of valoneoyl structures which are formed by C-O linkages between a hexahydroxydiphenoyl group and a galloyl group from an adjacent monomer [36]. The second typifies two C-O bond macrocyclic oligomers [36]. Distinct structural features and biosynthetic approaches help to differentiate the two major groups of hydrolysable tannins: gallotannins and ellagitannins [37]. A central glucose core distinguishes gallotannins, which are classified as type I hydrolyzable tannins. Their defining feature is a coalition of despotically linked galloyl groups. These compounds have more complex derivatives starting with their most simple precursor, β-glucogallin [38]. In contrast, ellagitannins, as Type II, III, and IV, are characterized by the presence of a polymeric dehydrodigalloyl unit, especially the hexahydroxydiphenoyl (HHDP) unit formed via oxidative coupling of galloyl moieties [39]. Type III ellagitannins, exemplified by geraniin, contain dehydrohexahydroxydiphenoyl (DHHDP) units, while type II consisting of tellimagrandins I and II incorporate HHDP units [40]. Type IV ellagitannins are further characterized by the presence of modified DHHDP units, such as chebuloyl or Elaeocarpus groups [41]. Both gallotannins and ellagitannins begin with β-glucogallin, but their respective biosynthesis pathways become quite distinct due to the unique structural features that each type boasts of [42]. Gallotannins are formed in a series of galloylation steps of β-glucogallin by first generating β-penta-O-galloyl-D-glucopyranose (β-PGG), which can then undergo further galloylation to form depside complex galloyl compounds. Conversely, β-PGG galloyl groups can intramolecularly oxidatively couple to yield HHDP units which is the basis for ellagitannins. These ellagitannins may undergo other oxidative modifications that give rise to more intricate structures such as demethylated HHDP (DHHDP) units of more complex and sophisticated variations [43]. Both kinds of tannins carry substantial biological activity, but researchers are paying closer attention to ellagitannins compared to gallotannins [44]. Gallotannins can be handy in battling those stress balls from the wrong kind of oxidants as well as invading micro bugs thanks to their super antioxidants and antibacterial strengths [45, 46]. But ellagitannins have a much broader set of powerful biological effects, things like being antibacterials and antivirals as well as guarding against tumors [47]. For instance, some special guys in a class of compounds called ellagitannins look super-duper good at fighting off some bad guys. A good example of this are compounds called vescalagin and castalagin. They are killing things like HIV and herpes simplex infections which are also known as HSV [48,49]. With its exceptional

efficiency and precision, HPLC (highperformance liquid chromatography) is a widely used technique for the separation, identification, and measurement of ellagitannins in plant extracts. UV-Vis or diode array detection (DAD) is usually coupled to HPLC for increased sensitivity and accuracy. DAD provides complete spectrum information [50], since many compounds can be identified at various wavelengths simultaneously. Nuclear magnetic resonance (NMR), especially 1HNMR and 13C-NMR, is a strong analytical technique used extensively for the structural elucidation of complex natural compounds like ellagitannins [51]. MS, which generates detailed structural knowledge, is a key tool for determining the size & fragmentation of ellagitannins. These sophisticated compounds are ionized using techniques including ionizing electrospray (ESI), along with matrix-assisted laser desorption/ionization (MALDI), which provide molecular and fragment ions to be analysed. While MALDI uses for larger molecules and sensitive molecules are more attractive ESI Stationary Phase [52]. UV-Vis spectroscopy is currently the most widely used optical method to identify and characterize ellagitannins, which absorb ultraviolet and visible wavelengths based on electronic changes in their structure. This method is essential in fields such as environmental studies, food science, and phytochemistry, as it enables researchers to identify and quantify ellagitannins from different matrices by analyzing their spectra of absorption [53].

RESULT:

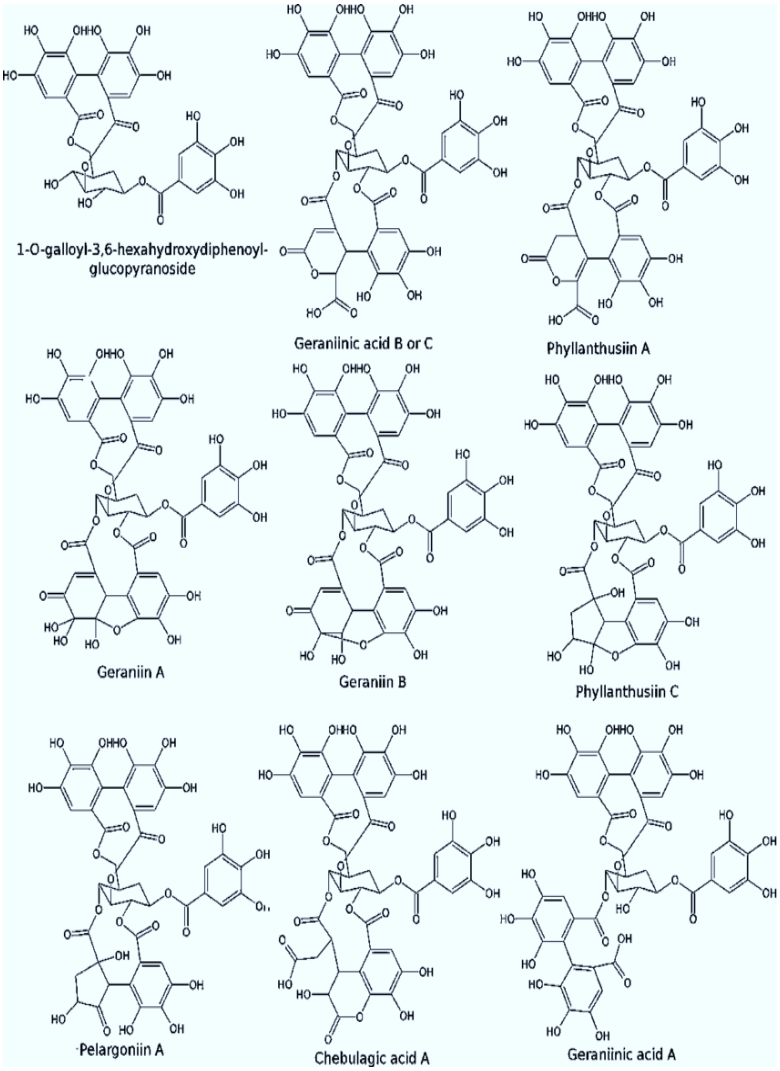

Figure No.: -1 **The Phyllanthus water-soluble extracts that were under investigation were believed to contain Ellagitannins [54].**

BIOSYNTHESIS OF ELLAGITANNINS IN PLANTS

The production of ellitannins is a group of hydrolyzable tannins using the shikimate pathway that is made by phenylpropanoid metabolism, gallic acid is the key substance that is formed

from 3-dehydroshikimate [55]. The conversion of 3-dehydroshikimate into gallic acid is the result of the catalysis of the major enzymes that include dehydroshikimate dehydratase and shikimate dehydrogenase [56]. When UDP-glucose: galloyl transferase enzyme esterifies gallic acid to glucose, then the β-glucogallin is generated. Subsequently, β-glucogallin is changed by galloyl transferases and ellagitannin-selective enzymes like laccases and oxidases to lead to complex ellagitannin structures [57]. Breakdown of ellagitannins through the oxidative coupling process is an indispensable part of their natural breakdown and is catalyzed by the laccase-like enzymes polyphenol, which are responsible for bonding the galloyl groups to HHDP units that are ellagitannin-specific. This is an evolved pathway that enlightens the coworking role of multiple enzymes in the synthesis of most significant polyphenolic compounds [58]. Ellagitannins are compounds that can be used in many ways to aid the plant in its defense against all living things and to gain flexibility which makes them very essential components in the ecological interactions and the plant defense. Not only their antimicrobial properties but they only fight against the growth of microorganisms such as viruses and fungi and infection is also overcome. Additionally, the astringent and the protein binding property of ellagitannins make the plant tissue unattractive and not easy to digest [59]. Potent antioxidants are substances that help to counteract the damaging effect of free radicals, "ROS," that are also known as reactive oxygen species at the cell levels. Thus, they are a cellular antecedent to a healthy life cycle of plants as they are also a radioprotectant. Apart from the above, they impact microbial communities and soil intelligence, all which influences plant-microbe relations, nutrient cycling, among other ecological processes in their niche environments [60]. The biosynthesis and accumulation of ellagitannins across the various plants are regulated by the environment and the individual genetic make-up of the plants. Thus, they also participate in the repair mechanism of those plants thus when exposed to environmental stresses (UV, dehydration, diseases infections, etc.), the production of ellagitannin is enhanced. Additionally, this process is greatly influenced by the availability of nutrients; a lack of nitrogen or phosphorus frequently results in a rise in the synthesis of phenolic compounds, such as ellagitannins [61]. Developmental stage also influences ellagitannin levels since younger tissues often contain more of them to provide greater protection during critical growth phases. Furthermore, biotic interactions such as herbivory and microbial infection can stimulate the formation of ellagitannin through signaling pathways including salicylic acid along with jasmonic acid [62].

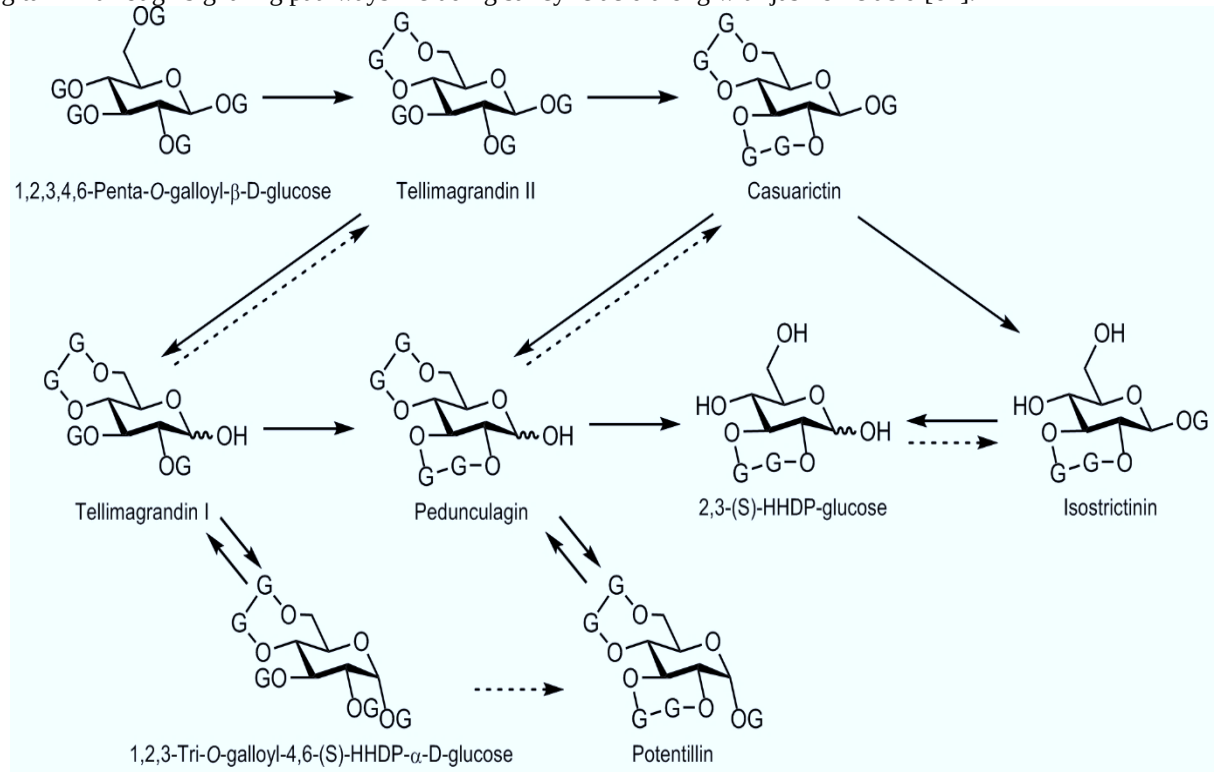

Figure No.: -2 **The first biosynthesis processes that produce ellagitannins starting from 1,2,3,4,6-penta-O-galloyl-beta-D-glucose. Galloyl units are denoted by the letter G, whereas HHDP units are denoted by the letter G-G [63].**

METABOLIC PATHWAYS OF ELLAGITANNINS IN ANIMALS AND HUMANS

Ellagitannins (ETs) possess a high molecular weight and intricate structure, resulting in poor absorption in their unaltered state. Instead, they undergo hydrolysis in the gastrointestinal tract, yielding ellagic acid (EA), which similarly has low absorption rates. Therefore, the availability of both ETs and EA is mainly limited because most of the substances that are ingested reach the colon. Under these conditions, the microorganisms found in the gut are important for the degradation of these chemicals into active metabolites such as urolithins. These metabolites are then distributed and excreted demonstrating the vital role of microbial action in the release of health benefits related to ETs [64,65]. Evidently, the gut microbiota is essential in the biotransformation of ellagitannins and ellagic acid, as they are rendered to be more bioavailable and biologically active metabolites by them, i.e. urolithins (including urolithin A, urolithin B, and urolithin C) through various dihydroxylation and decarboxylation processes. Urolithin A, as a product, has been the subject of most studies. The effectiveness and the extent of the metabolic conversion are dependent on the gut microbiota composition, which is acknowledged as the main source of urolithin synthesis variability among people [66,67]. The bioactive metabolites of ellagitannins & ellagic acid, specifically urolithins, are transported to particular tissues and organs after absorption. In these sites, they develop a set of biological actions that include anti-inflammatory, antioxidant, & anticancer effects [68]. These bioactivators were mainly excreted following digestion and the genetic factors of the individual, as well as the form in which urolithin was absorbed would also significantly contribute to the differences in the elimination patterns of the metabolites [69]. The relatively rapid absorption and distribution of urolithins can be shown by the fraction that they primarily are present in both blood and urine within the period of a few hours following ingestion [70]. The additional biological function of urolithin A may be due to its longer half-life compared to other metabolites such as urolithin B and urolithin C. Individual genetic differences, gut microbiota composition, and dietary choices all influence urolithin metabolism as well as excretion, highlighting the complexity of ellagitannin metabolism in humans [71].

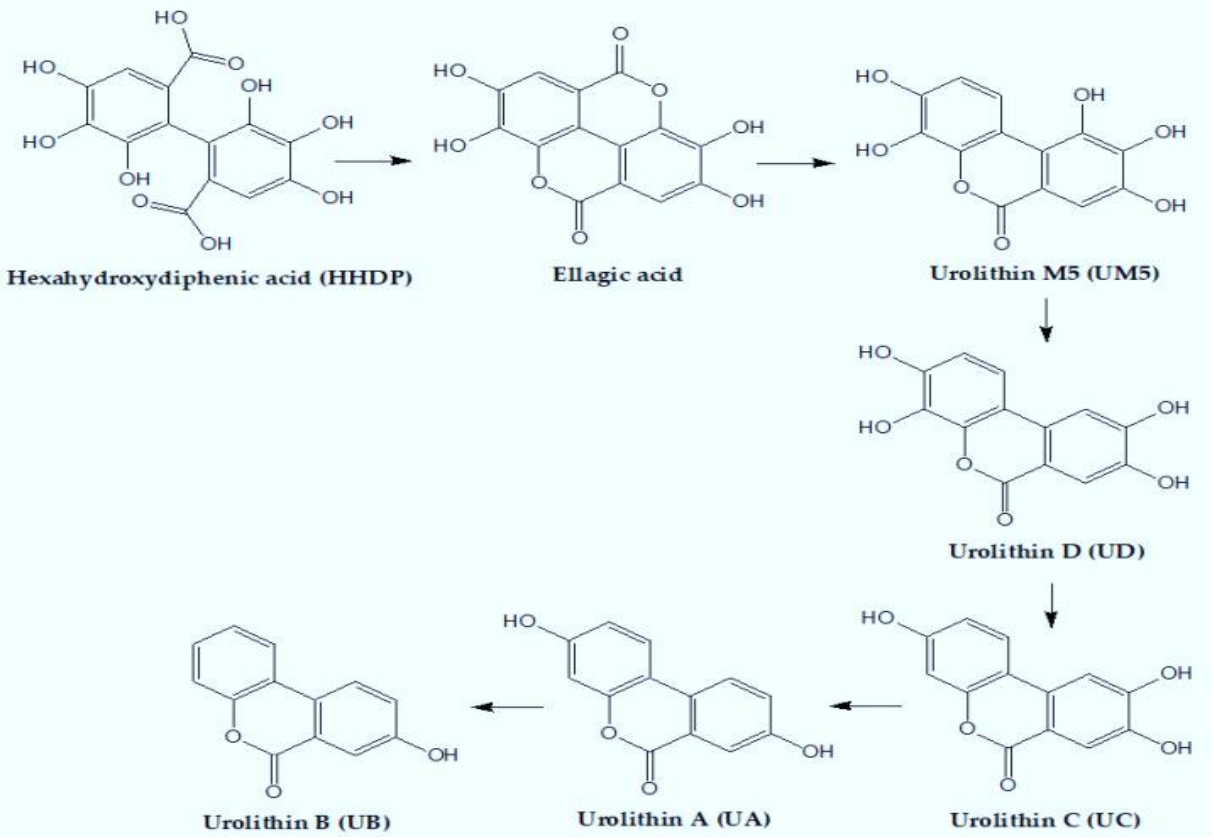

Figure No.: -3 Some of these are urolithins, which are ellagic acid compounds that the Produced by the microbes [72].

HEALTH BENEFITS OF ELLAGITANNINS AND THEIR METABOLITES

Table No.: -1 Overview of the Health Advantages, Action Mechanisms, and Disease Prevention/Treatment of Ellagitannins & Their Metabolites

Ellagitannin Type	Health Benefit	Mechanism of Action	Disease Treatment/Prevention	Reference
Punicalagin	Anti inflammatory & antioxidant qualities	Blocks the NF-κB pathway and scavenges free radicals	lowers inflammation and oxidative stress in chronic illnesses	[73]
Urolithin A (Metabolite)	Modulation of the microbiota and gut health	Improves the function of the intestinal barrier and encourages the development of good bacteria	Enhances intestinal health and guards against inflammatory bowel disease (IBD).	[74]
Ellagic acid	Possible anticancer properties	Promotes apoptosis and suppresses the proliferation of tumor cells	Lowers the likelihood of developing colon, prostate, and breast cancer	[75]
Gallagic acid	Cardiovascular health advantages	Enhances lipid metabolism and lowers LDL cholesterol levels	Helps prevent atherosclerosis and cardiovascular conditions	[76]
Urolithin B (Metabolite)	Neuroprotective Benefits	Decreases neuroinflammation and prevents the aggregation of amyloid-beta.	Offers protection against Alzheimer's and Parkinson's diseases.	[77]
Castalagin	Antioxidant Characteristics	Counteracts reactive oxygen species (ROS)	Lowers the risk of diseases associated with oxidative stress (such as diabetes and aging)	[78]
Vescalagin	Anti inflammatory characteristics	Inhibits the activity of COX-2 and iNOS enzymes	Alleviates inflammation associated with arthritis and various other inflammatory disorders	[79]
Urolithin C (Metabolite)	Gut health and microbiome	Regulates gut microbiota and enhances the	Promotes metabolic well-being and helps	[80]

	regulation	presence of Akkermansia muciniphila	prevent obesity	
Pedunculagin	Anticancer Properties	Promotes cell cycle inhibition and programmed cell death in malignant cells	Lowers the likelihood of developing liver and lung cancer	[81]
Sanguiin H-6	Cardiovascular health advantages	Enhances endothelial performance and lowers blood pressure	Averts hypertension and cardiovascular disease	[82]
Urolithin D (Metabolite)	Neuroprotective Benefits	Improves mitochondrial performance and diminishes oxidative stress within neurons	Offers protection against neurodegenerative disorders	[83]
Tellimagrandin I	Antioxidant and anti inflammatory characteristics	Suppresses the generation of reactive oxygen species (ROS) and pro-inflammatory cytokines	Alleviates inflammation associated with autoimmune disorders	[84]
Casuarictin	Gut health and microbiome regulation	Encourages the proliferation of Lactobacillus and Bifidobacterium	Enhances gut health and helps prevent dysbiosis	[85]
Geraniin	Anticancer Properties	Prevents the formation of new blood vessels and the spread of tumors	Lowers the likelihood of developing skin and stomach cancer	[86]
Urolithin A (Metabolite)	Cardiovascular health advantages	Decreases arterial rigidity and enhances lipid levels	Averts atherosclerosis and promotes heart wellness	[87]
Punicalin	Antioxidant Characteristics	Neutralizes free radicals and boosts the activity of internal antioxidant enzymes	Lowers oxidative stress associated with aging and metabolic conditions	[88]
Ellagitannin rich extract	Neuroprotective Benefits	Decreases neuroinflammation and improves synaptic	Safeguards against cognitive deterioration and dementia	[89]

		plasticity		
Urolithin B (Metabolite)	Gut health and microbiome regulation	Enhances the synthesis of short chain fatty acids (SCFAs)	Promotes gut well being and lowers the likelihood of colorectal cancer	[90]
Oenothein B	Anti inflammatory characteristics	Suppresses the production of TNF-α and IL-6	Alleviates inflammation associated with chronic inflammatory conditions	[91]
Urolithin C (Metabolite)	Cardiovascular health advantages	Enhances endothelial performance and diminishes oxidative stress within blood vessels	Averts endothelial dysfunction and the onset of cardiovascular diseases	[92]

ELLAGITANNINS IN ANIMAL HEALTH

Ellagitannins, a class of hydrolyzable tannins, has shown great potential in promoting immune system and improving growth performance of cattle and poultry. They function as normal growth promoters and antioxidants by increasing food absorption, regulating gut flora, and improving physiological situations. Overall, these advantages enhance animal growth rates & meat quality, particularly for broilers [93]. In addition, these compounds also possess immunomodulatory properties that can enhance the general health and resilience of the animals through reduction of inflammation & oxidative stress. Moreover, because they can alleviate oxidative stress, they can perhaps help intestinal health, hence promoting the productivity and well-being of cattle and poultry [94]. Ellagitannins and their derivatives, such as ellagic acid, are considered promising substances in veterinary medicine because of their numerous therapeutic properties. The powerful antibacterial, antifungal, antiviral, and antiparasitic activities of these compounds make these natural oils effective agents for the treatment of infections and improving general animal health [95]. Moreover, it is well known that ellagitannins possess strong hepato-protective, cardioprotective, antioxidant, as well as antiinflammatory qualities which can reduce inflammation, oxidative stress, and organ damage in animals. They may be used as natural alternatives to veterinary therapies to cure a variety of illnesses and improve the wellbeing of livestock and poultry because of their many benefits [96,97]. Ellagitannins are important for animal nutrition and feed supplements as they have many aspects that can improve animal health and productivity [98]. Eating organic fodder not only enhances the metabolic processes of food but also limits the pathological intestinal bacteria, thereby, ensuring the quality of food products like meat, milk, and eggs is maintained. Under the effect of these phytochemicals, methane release can be reduced, and hence more nutrients can be utilized to produce less harmful greenhouse gas emissions and byproducts [99]. Similarly, by involving microbiological protein synthesis in the rumen and reducing rumen protein breakdown, ellagitannins in ruminants can be further optimized to achieve sustainable livestock production. Natural extracts are developed as a substitute for synthetic growth stimulants, and they have been shown to have the same positive effect as they boost milk production, growth rates, and total livestock productivity [100]. Moreover, they are also a great means for successful animal nutrition and the conservation of nature.

ELLAGITANNINS IN HUMAN NUTRITION AND DISEASE PREVENTION

A class of water-soluble tannins known as ellagtannins (ETs) is found in many different plantbased foods and is thought to have potential advantages for dietary intake and illness prevention. In addition to pomegranates, they can also be found in fruits like cloudberries, berries like rasp blackberries, and strawberries, as well as nuts like almonds and walnuts, which are pecans [101]. Additional sources include teas, several medicinal plants, along with wines

that have been aged in oak barrels. There is no specific daily recommended intake for ellagitannins; however, dietary guidelines such as the Mediterranean way of life or DASH habits of eating, which emphasize a high intake of fruits, nuts, and vegetables, can help ensure that these compounds are consumed in adequate amounts. According to research, eating 1-2 servings of foods high in ellagitannin each day, including a limited number of berries and nuts, may have major health advantages [102,103]. Because of their anti-inflammatory, anticarcinogenic, and antioxidant qualities, Ellagitannins (ETs) with their metabolites, including urolithins, are important in the prevention of chronic illnesses. They prevent postprandial blood sugar rises in diabetics by lowering blood glucose, improving insulin sensitivity, and inhibiting enzymes that break down carbohydrates, such as α-glucosidase and α-amylase [104]. In the case of obesity along with metabolic syndrome, ellagitannins alter the composition of the gut microbiota, decrease adipogenesis, encourage the darkening of white adipose tissue, and modify lipid metabolism, all of which contribute to improved metabolic health [105]. Ellagitannins lower blood pressure, improve endothelial function, lessen oxidative stress, and prevent the oxidation of LDL cholesterol, which is a key cause of atherosclerosis [106]. Ellagitannins have anti-cancer effects in at least two ways. First, they modify (in a way that lowers cancer risk) important biological signaling pathways that are linked to cell growth, tumor formation, and tumor metastasis (spreading). Second, ellagitannins induce (trigger) in cancer cells anti-proliferative (stop cell division) and pro-apoptotic (start the programmed death of the cell) reactions [107]. The synergistic effects of ellagitannins with other dietary polyphenols, such as flavonoids, phenolic acids, and anthocyanins, often enhance the overall bioactivity of ellagitannins. For example, the combination of ellagitannin and anthocyanin in berries offers much greater protection against oxidative stress than any single antioxidant [108]. If that is the case for two compounds that are taken together, think how much more powerful the effect should be when three, four, or even five compounds that happen to reside in the very same biological place are taken together. Let us not forget the very prime target of potential damage by free radicals: DNA [109]. Ellagitannins and the flavonoid quercetin also enhance their anti-inflammatory actions by modifying (in a way that reduces cancer risk) important biological signaling pathways that control inflammation. These complementary relationships emphasize how crucial it is to eat a variety of foods high in polyphenols to optimize health benefits [110].

CHALLENGES AND LIMITATIONS IN ELLAGITANNIN RESEARCH

Table No.: -2 The table lists the difficulties encountered in ellagitannin research along with the solutions suggested.

Challenge	Details	Strategies to Overcome	References
Variations in bioavailability and metabolism across individuals	Ellagitannins undergo metabolism by gut microbiota, resulting in the formation of urolithins. The production of these compounds varies significantly due to the differences in individual gut microbiomes, which in turn influences their bioavailability and effectiveness.	To address this, personalized strategies can be employed, including the identification of specific metabotypes and the customization of dietary or probiotic interventions aimed at improving urolithin production.	[111]
Challenges in the Isolation and Study of Ellagitannins	Ellagitannins are intricate compounds, which complicates their extraction and purification from natural sources,	There is a need for the advancement of more effective methods for extraction and purification, including the	[111]

	necessitating labor intensive processes and sophisticated techniques such as HPLC and LC MS.	implementation of cutting edge chromatography techniques and the optimization of solvent systems.	
Possible adverse effects or toxicity associated with elevated doses	Elevated doses of ellagitannins or their metabolites could result in gastrointestinal discomfort or other adverse reactions, although information regarding toxicity is scarce.	It is essential to perform thorough toxicological research to determine safe dosage limits and to investigate encapsulation methods that can regulate release and reduce side effects.	[112]
Limited bioavailability in humans	Ellagitannins exhibit low solubility and stability within the gastrointestinal system, resulting in restricted absorption.	Enhancing the formulation of ellagitannins with bioenhancers or employing nanotechnology-driven delivery systems can improve their solubility and stability.	[112]
Absence of standardized analytical procedures	The inconsistency in analytical techniques results in variable outcomes when quantifying and characterizing ellagitannins.	Establishing standardized protocols for ellagitannin analysis, which encompass validated methods for HPLC and LC-MS, is essential.	[111]
Insufficient Clinical Research	The majority of studies on ellagitannins are preclinical, with a scarcity of human trials to substantiate their health advantages.	It is essential to carry out rigorously designed clinical trials to confirm preclinical results and establish health claims based on solid evidence.	[97]
Degradation in Food Processing	Ellagitannins are susceptible to alterations in temperature and pH, resulting in their degradation throughout food processing.	It is essential to optimize food processing conditions to maintain ellagitannin levels and to investigate encapsulation methods that can safeguard these compounds.	[97]
Extraction and purification are expensive.	It takes a lot of money and effort to extract and purify ellagitannins from natural sources.	investigating economical extraction techniques, such enzymatic hydrolysis or the use of agricultural byproducts.	[97]
Insufficient comprehension of action mechanisms	We don't completely understand the precise processes by which ellagitannins provide their health advantages.	employing cutting-edge molecular biology methods to carry out mechanistic investigations to clarify targets and processes.	[112]
Effects of extraction procedures on the environment	The extraction of ellagitannin using organic solvents may have adverse effects on the environment.	establishing sustainable practices and creating green extraction techniques, such as employing ethanol or water as solvents.	[97]

TECHNOLOGICAL AND INDUSTRIAL APPLICATIONS

For industrial use, ellagtannins—polyphenolic substances included in pomegranates, berries, nuts, & wines aged in oak barrels—need to be extracted and purified effectively [113]. To successfully separate ellagitannins from plant materials, common extraction techniques include solvent extraction employing ethanol, methanol, or acetone, frequently in aqueous solutions [114]. Though supercritical fluid extraction (SFE) using CO_2 provides an environmentally friendly method that prevents thermal degradation, advanced approaches like ultrasoundassisted extraction (UAE) increase efficiency by breaking down cell walls, boosting yield, and decreasing extraction time [115,116]. By facilitating quick extraction with less solvent usage, microwave-assisted extraction (MAE) significantly increases efficiency [117]. In addition to membrane filtering methods like ultrafiltration & nanofiltration, that separate ellagitannins according to molecular weight, column chromatography employing silica gels, Sephadex LH-20, and polyamide resins is frequently used for purification [118,119]. High purity ellagitannin separation and accurate quantification are achieved using high-performance liquid chromatography (HPLC), guaranteeing its successful use in a variety of sectors [120]. Because of their strong antibacterial, anti-inflammatory, and antioxidant qualities, Ellagitannins are being used more and more in dietary supplements, nutraceuticals, and functional foods [121]. They are added to drinks, yogurts, and snacks as part of functional foods; pomegranate juice & berry extracts are common sources [122]. Because of its potential to improve gut microbiota, lower oxidative stress, and boost cardiovascular health, ellagitannins are marketed as nutraceuticals and are made into capsules, pills, and powders [123]. One of the myriad health benefits of these compounds is their potent antioxidant activity, which effectively combats free radicals and mitigates oxidative damage. Furthermore, these compounds transform into urolithins, which exhibit remarkable anti-inflammatory and anti-cancer properties, thereby promoting gut health. In addition to these advantages, ellagitannins contribute to cardiovascular protection by enhancing endothelial function and lowering blood pressure, establishing them as a vital ingredient in health-focused products [124,125]. The use of ellagitannins in cosmetics is on the rise because of their anti-aging, antioxidant, and skin-protective abilities. Anti-aging treatments act to protect the dermal layer from UV filtration whilst also decreasing wrinkles by slowing down the degradation process of collagen, thus improving the complexion and providing a more youthful appearance [126]. Ellagitannins are additionally utilized for skinwhitening formulations to treat hyperpigmentation and to decrease melanin production by inhibiting tyrosinase activity [127]. They are also good for people with sensitive skin due to their anti-inflammatory properties, as they can help to calm and protect the skin while reducing irritation and redness [128].

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

The vast scope of biological activities and probable health benefits from Ellagitannins (ETs) are being increasingly appreciated. Research progress on ellagitannin now features high sophistications of analytical methods, omics technologies, nanotechnology delivery systems, and green extraction techniques. The composition of the gut microbiota is important for ellagitannin metabolism, which enhances the possibility of custom tailoring dietary strategies. Furthermore, advances in genome sequencing and metabolomics allow the deeper analysis of gut microbiota so to help predict metabolic capabilities and recommend personalized nutrition. To mitigate the metabolic effects of gut flora and maximize the health benefits of ellagitanninrich diets, tailor made individual diets using specific probiotics and prebiotics can be designed. Ellagitannins together with other metabolites bears huge medicinal possibilities with ongoing investigation for novel applications. These include neuroprotective agents for neurodegenerative diseases and anticancer drugs where urolithins induce apoptosis and inhibit tumor growth. Potential for the treatment of antibiotic-resistant infections is also considered in ellagitannins.

CONCLUSION

The applications of powerful bioactive substances like ellagic tannins (ETs) and their metabolites, particularly urolithins, seem to have no limit, as they can be utilized by both humans and animals alike. These hydrolyzable tannins have found applications in alleviating inflammation, treating cancer, antibacterial activity, plus antioxidant functions, and are present in several nuts, fruits, and even medicinal plants. In the gastrointestinal tract, ETs undergo hydrolysis whereby ellagic acid is released and subsequently transformed into urolithins by the gut microbes. Research shows that they may help prevent and manage some chronic illnessessuch as cancer, diabetes, heart disease, and neurological disorders. Moreover, they improvegrowth performance, strengthen immunological responses, and

promote gastrointestinal health,making them efficacious and healthy alternatives to synthetic growth promoters. Chronicillnesses can be avoided by ETs through reducing oxidative stress, inflammation, andmetabolism. They also enhance the function of gut barriers and promote beneficial flora makingthem ideal for sustainable livestock production. More studies and innovations are needed to overcome challenges of clinical evidence, gaps in data, extraction and purification problems, and variability in bioavailability.

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Authorship Contribution
Bipin Singh-Conceived the review idea, designed the manuscript structure, conducted the primary literature analysis, data curation, and wrote the original draft. Suraj Bansal-Supervised the project, provided overall guidance, and performed the final review and approval of the manuscript for publication. Rakesh Chawla-Contributed to the writing and critical revision of the manuscript, with a focus on classification, biosynthesis, and metabolic pathways. Maneesha Bhardwaj- Assisted in data collection, literature review, and contributed to the drafting of specific sections, particularly on health benefits and industrial applications. Krati Dhakad-Participated in data organization, literature synthesis, and provided critical intellectual input during the editing and finalization of the content. All authors have read and approved the final version of the manuscript submitted for publication.

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