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Review Article

Dentistry Section

Raspberries: An Aggregation of its Bioactive Constituents- A Narrative Review

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ABSTRACT

According to the available literature evidence, regular consumption of fruits and vegetables is inversely proportional to the risk of developing certain types of cancer. Berries, such as raspberries, have a higher rate of antioxidants, anti-inflammatory properties, and chemopreventive properties. These attributes make them useful in the treatment of certain chronic diseases and cancer prevention. Raspberries are enriched with phytochemicals, with polyphenols being the major phytochemical present. These polyphenols include ellagitannins (tannins), phenolic acids, anthocyanins (flavonoids), catechins (flavonoids), and proanthocyanins (flavonoids). Available evidence indicates that natural extracts have no side effects, no drug interactions, and can be safely used in all populations, including pregnant women and children. Therefore, the utilisation of natural products for disease treatment is always encouraged. Berry fruits consistently rank among the top sources of total phenolics and Antioxidant Capacity (AOC), containing levels up to four times greater than other fruits. The polyphenolic compounds in raspberries play a significant role in mitigating the damaging effects of oxidative stress on cells and reducing the risk of chronic diseases such as cardiovascular diseases, type 2 diabetes, obesity, age-related neurodegenerative diseases, and infection-associated neurodegenerative diseases.

Keywords: Anthocyanins, Antioxidant properties, Polyphenols

INTRODUCTION

Health is defined as a state of well-being in terms of physical, mental, and psychosocial status [1]. Many factors can affect health, including hereditary predisposition, socio-economic status, microbial infections, and lifestyle practices. When one or more of these factors impact a person's physical, mental, or psychosocial status, the term "diseased" is used to describe their debilitating condition [2]. Although the likelihood of developing a disease is not entirely within human control, efforts have been made to prevent and cure them. However, the question remains when it comes to diseases caused by lifestyle practices [3]. The nourishment required by the human body can be broadly categorised as macronutrients and micronutrients. Poor dietary habits have deprived humans of the daily required nutrients necessary for optimal cellular functioning at the molecular level and to protect cells from transient, highly unstable byproducts that can cause irreversible damage [4]. Fruits, green leafy vegetables, and colourful vegetables naturally contain these macronutrients and micronutrients, along with unique organic compounds called phytochemicals [5].

Raspberries belong to the rose family, genus Rubus, and come in various colours such as red, black, yellow-pink, and purple. There are 12 subgenera and over 500 species of raspberries [6]. The nutrient content of raspberries can be influenced by cultivation methods, soil characteristics, ripeness, and shelf life [7]. They are enriched with phytochemicals, which are non nutritive compounds produced through secondary metabolism to provide protection to the plant from Ultraviolet (UV) radiation, predator pests, and to regulate chemical pathways [8]. The objective of the current review is to provide a detailed analysis of the various phytochemicals present in raspberries and their characteristics, particularly focusing on their potential applications in the field of medicine. A literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar. Additionally, a hand search was performed to find relevant articles. The retrieved articles were evaluated to extract the necessary information.

Phytochemicals of Raspberry

The biosynthesis of phytochemicals is initiated in the rough endoplasmic reticulum, which depends on the secondary metabolites produced within the plastids during the shikimate pathway [9]. In a study conducted by Chen L et al., the phytochemical properties of 15 commercially available varieties of raspberries were compared to their antioxidant capacity [10]. They observed that higher phytochemical content corresponded to a more potent antioxidant capacity. Polyphenols, including ellagitannins (tannins), phenolic acids, anthocyanins (flavonoids), catechins (flavonoids), and proanthocyanidins (flavonoids), are the major phytochemicals in raspberries [11,12].

a) Ellagitannins: Ellagitannins contribute to the major antioxidant properties of raspberries. They are hydrolysable esters of Hexahydroxydiphenic acid (HHDP) and glucose or quinic acid, which, when hydrolysed, yield ellagic acid (a dimeric derivative of gallic acid) [13]. Common forms of ellagitannins in raspberries include sanguiin H6 (dimer), sanguiin H10, and lambertianin C (trimer). Sanguiin H6 and lambertianin C remain stable even during six months of storage and in processed food forms. Ellagic acid is abundant in the pulp and seeds of raspberries but less in the juice [14]. The molecular size of ellagitannins ranges from above 634 Da (sanguiin H4) to 3740 Da (lambertianin D). While most ellagitannins are hydrolysed to free ellagic acids in the duodenum, certain forms of ellagitannins are resistant to digestive acidic and alkaline hydrolysis in the gastrointestinal tract. They are also less soluble in water, limiting their bioavailability [13,15]. However, they are metabolised by the microbiota in the lower gastrointestinal tract into urolithin A, urolithin B, urolithin C, and urolithin D, which are detectable in the plasma and urine of individuals who consume raspberries [15]. In a study, a single dose of 300 grams of red raspberries resulted in the presence of urolithin A and urolithin B in the plasma for more than 24 hours and up to 48 hours in urine after ingestion [16].

b) Phenolic acids: Phenolic acids can be broadly classified as hydroxybenzoic acids, hydroxyphenylacetic acids, and hydroxycinnamic acids. They are present in small quantities, with caffeic acid, ferulic acid, p-coumaric acid, and chlorogenic acid being common phenolic acids found in raspberries [17]. Chlorogenic acid, ferulic acid, and other plant cell wall-bound hydroxycinnamic acids require enzymatic action of the colonic microflora for metabolism in humans [18].

c) Anthocyanins: These phytochemicals are derivatives of 2-phenylbenzopyrylium, containing two benzoyl rings separated by a heterocyclic ring, which impart diverse shades of color to plants, flowers, and fruits [19]. The daily average intake of anthocyanins depends on dietary habits and the quantity of anthocyanins in the consumed food, which can vary from a few milligrams to hundreds [20]. Unlike ellagitannins, the metabolism of anthocyanins is initiated in the upper gastrointestinal tract and does not require the assistance of colonic microbiota [21]. Cyanidin-3-O-glucosylrutinoside, cyanidin-3-O-sophoroside, cyanidin-3-O-glucoside, pelargonidin-3-sophoroside, pelargonidin-3-O-glucosylrutinoside, pelargonidin-3-glucoside, and pelargonidin-3-rutinoside are the major forms of anthocyanins in red raspberries. Cyanidin-3-rutinoside (C3R), Cyanidin-3-glucoside (C3G), and Cyanidin-3-xylosylrutinoside (C3XR) are the major bioactive anthocyanins in black raspberries [22,23].

d) Catechins: The name catechins is derived from the word catechu, an extract of acacia trees [24]. They exist in two steric forms: trans {(+)-catechins) and cis ((-)-epicatechin} configurations, and raspberries are rich in epicatechins [25]. Absorption of catechins in the human body occurs in the small intestine. Regardless of the steric form of catechins consumed, epicatechin-3'-O-glucuronide is the sole metabolite present in the plasma, although their concentrations may differ between the two steric forms [26].

e) Proanthocyanidins: These are formed as a result of the condensation of flavan-3-ols catechin and epicatechin into tannins. They provide protection to plants from biotic and abiotic stressors and are produced through the same biosynthesis pathway as anthocyanins, with variations in concentration throughout the developmental stages [27]. Procyanidins, which are derived from proanthocyanidins, are oligomeric derivatives of epicatechins and are categorised as type A and type B based on their carbon skeleton [25,28]. Procyanidins form complexes with carbohydrates, proteins, and fats present in the plant and can complicate their extraction [28]. Monomers of proanthocyanidins are absorbed from the proximal intestinal tract, while their oligomers and polymers are acted upon by the gut microbiota [29].

Salient Properties of Phytochemicals in Raspberries

The health benefits of raspberries are credited to their rich phytochemical composition. Each of these phytochemicals exerts its own effect on the human body, and many studies are being carried out to exploit their medicinal properties for better healthcare services [8,10,14,20,23,25].

Antioxidant Properties

Imbalance between the production and accumulation of Reactive Oxygen Species (ROS) in cells, and the biological system's ability to detoxify these ROS, is called oxidative stress [30]. This can impair cellular health and lead to life-threatening diseases. The individual antioxidant properties of all the phytochemicals present in raspberries can help combat oxidative stress in humans. Wolfe KL et al., found that raspberry extract has one of the highest cellular antioxidant activities among 25 commonly consumed fruits [31]. Similarly, in 2010, Bowen-Forbes CS et al., analysed the properties of blackberry and raspberry fruits compared to four other fruits [32]. They concluded that the anthocyanins in black raspberries exhibited the highest inhibitory activity against lipid peroxidation when compared to the other fruits included in the study.

Anti-inflammatory Properties

A pathogen, injury, or damage can trigger inflammation as a self-defense mechanism by the cells. However, when inflammation becomes chronic, it can cause damage to Deoxyribonucleic Acid (DNA), macromolecules, tissues, and lead to the accumulation of reactive oxygen species, resulting in increased oxidative stress [33]. In their experiment, Bowen-Forbes CS et al., found that anthocyanins had the ability to downregulate the cyclo-oxygenase 2 pathway, which is an indicator of an active inflammatory process [32]. They emphasised the possible anticancer activity of anthocyanins. In a laboratory study that simulated collagen-induced arthritis using a rat model, administration of 15 mg/kg of red raspberry extract significantly resolved the development of clinical signs of arthritis and reduced soft tissue swelling, the amount of bone resorption, and the formation of osteophytes, thereby preventing the risk of articular destruction [34].

Anticancer Properties

In 2008, Seeram NP et al., conducted a test on the antiproliferative activity of extracts from blackberry, black raspberry, red raspberry, blueberry, strawberry, and cranberry on human cancer cell lines including colon, breast, oral, and prostate. They also evaluated their proapoptotic activity using a human colon cancer cell line [35]. The researchers observed that the antiproliferative activity of all the berry extracts increased with higher concentrations, and black raspberry extract induced three times more apoptosis compared to the others. They attributed this apoptotic effect on human cancer cell lines to the presence of anthocyanins, which they claimed to be the major contributor [35]. Additionally, Tulio AZ Jr et al., suggested that the high phenolic content of black raspberries and their strong antioxidant effects contribute to their anticancer properties. These properties include the ability to regulate the expression of oncogenes, enzymes that control cell cycling and proliferation, promotion of apoptosis in cancer cells, and inhibition of the invasiveness of tumour cells [36].

Antimicrobial Properties

In 2014, Krstic´ TP et al., analysed the inhibitory effects of ethanol and ether extracts of raspberries on eight Gram-positive bacteria: *Staphylococcus aureus*, *Staphylococcus aureus* ATCC 11632, *Streptococcus agalactiae*, *Rhodococcus equi*, *Rhodococcus equi* ATCC 6939, *Arcanobacterium pyogenes*, Arcanobacterium haemolyticum, and *Enterococcus* spp. They also tested six Gram-negative bacteria: *Pseudomonas aeruginosa*, *Pseudomonas aeruginosa* ATCC 10145, *Escherichia coli*, *Salmonella Enteritidis*, *Salmonella Typhimurium* ATCC 14028, and *Klebsiella* spp., as well as the fungus *Candida albicans* and the algae *Prototheca wichermanii* [37]. The study revealed that the ethanol extract of raspberries exhibited strong antibacterial activity against Gram-positive bacteria, moderate antifungal activity against *Candida albicans* when using raspberry juice, and poor inhibitory effects when using the methanol extract of raspberry [37].

In a recent study by Messaoudi O et al., a virtual experiment was conducted to assess the inhibitory effects of anthocyanins extracted from different berries on the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) main protease and SARS-CoV-2 spike glycoprotein using the molecular docking method and a favourable target site. They found that pelargonidin-3-glucoside, a subclass of anthocyanin found in raspberries, inhibited the bonding of SARS-CoV-2 with Angiotensin-converting Enzyme 2 (ACE2) receptors in host cells [38].

Antiobesity Properties

Using an animal study model, Wu T et al., evaluated the efficacy of raspberry anthocyanins in preventing diet-induced obesity. They administered a low-fat and high-fat diet with raspberry anthocyanins at a dosage of 200 mg per kg of diet to three study groups of mice for 12 weeks [39]. The researchers observed that after 12 weeks of raspberry anthocyanins consumption, there was a 63.7% reduction in body weight gain compared to the control group. Additionally, there were reductions in serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, hepatic lipid levels, and serum malondialdehyde, along with increases in serum superoxide dismutase and glutathione peroxidase [39].

The mouse preadipocyte 3T3-L1 cell culture was used to study the effect of freeze-dried raspberry extracts at varying concentrations on lipogenesis [40]. The study showed that raspberry extracts significantly downregulated the expression of proinflammatory mediators such as interleukin-6, monocyte chemoattractant protein 1, and interleukin-1β. Conversely, it upregulated interleukin-10 expression, which in turn increased lipid metabolism [40].

In 2022, Popovic T et al., conducted a human intervention study involving 20 women of reproductive age to evaluate the effects of consuming blueberry and raspberry pomace-based cookies for a duration of four weeks [41]. The study found a 25.52% increase in the level of serum adiponectin and a significant reduction in serum levels of saturated fatty acids [41].

Oral Health Application

In 2008, Mallery SR et al., conducted a human clinical trial on 32 patients with oral premalignant lesions resulting from tobacco product usage. The trial aimed to assess the effect of topically applying a 10% freeze-dried black raspberry gel on these lesions using histopathological findings and histochemistry profiles [42]. Comparing their histopathological results to a previous study on the topical application of 13-cis retinoic acid, IFN-α, and α-tocopherol on oral and laryngeal premalignant lesions, a 35% decrease in intraepithelial neoplasia was observed with the use of freeze-dried black raspberry gel, compared to only 14% with the other topical preparations. The overall transcriptional activity was diminished, resulting in fewer biochemically active cells and reduced expression of cyclooxygenase 2 and inducible nitric oxide synthase proteins at the site of epithelial dysplasia [42].

Similarly, in 2015, 4.3g of freeze-dried black raspberry troches were administered to 38 patients with oral squamous cell carcinoma. Biopsies of the cancer tissue were obtained before the clinical trial and after the completion of the troches course [43]. The study showed downregulation of anti-apoptotic transcriptional biomarkers and inhibition of proinflammatory transcriptional biomarkers. In preclinical evaluation, topical application of freeze-dried black raspberries on high-risk mucosa of hamster cheek pouches showed a reduction in tumour incidence, squamous cell carcinoma multiplicity, and proliferation rate [44].

In 2018, Dutreix L et al., prepared eight extracts of both ripe and unripe raspberries using n-hexane, ethyl acetate (EtOAc), 1-butanol, and aqueous base. The effects of these extracts on *Candida albicans*, Candida Parapsilosis, and Candida glabrata were studied [45]. The researchers found that the hexane and ethyl acetate extracts of ripe red raspberries were most active against *Candida albicans* biofilm and had an antiadhesion effect on *Candida albicans*. Raspberry leaf extracts have been utilised and proven effective in reducing the symptoms of oral lichen planus [46]. The polyphenols proanthocyanidin, anthocyanin, and flavonol glycoside possess anti-aggregation properties, thus helping in the prevention of plaque accumulation in the oral cavity [47]. Raspberry extracts play a remarkable role in the management and prevention of various oral lesions and conditions [48].

DISCUSSION

The sustenance of life on Earth and the evolution of its inhabitants have been made possible solely by nature's diverse resources, which provide nourishment for living beings either directly or indirectly. Plants, occupying the first trophic level in the food chain, biosynthesise various macro and micronutrients from the environment, which are then consumed by other living creatures for their survival [49]. The nutrient content of each plant taxonomy is unique, with negligible to distinct differences within each taxonomical sub-classification, making some plants edible and others poisonous to living beings [50]. The indigeneity of various plants has limited their access to mankind. However, with the advancement of human civilisation, transportation systems, trade of goods, and exponential growth in technology, research, and biotechnology, the exploitation of various indigenous plants has become feasible. In the early 90s and late 20s, hybrid vegetables and fruits gained huge acceptance among people. However, the trend has now shifted towards "organic" and "farm fresh" vegetables and fruits [51]. This change is due to the belief held by many scientists that most of the current human illnesses are the result of lifestyle practices [52].

Scientists have been exploring the natural remedies present in various parts of plants. This literature review highlights the composition and properties of raspberries, which belong to the genus Rubus of the rose family.

Raspberries, apart from other macro and micronutrients, are a rich source of phytochemicals. Phytochemicals are bioactive non nutrient chemicals found in plant-based foods that may provide desirable health benefits and reduce the risk of major chronic diseases [53]. Raspberries have significantly higher content of phytochemicals compared to other berries, with polyphenols being the major phytochemical in raspberries [10,11]. Polyphenols in raspberries have been extensively researched in the field of medicine to combat various chronic diseases caused by inflammatory-mediated molecular impairments in the human body's biological functioning. These polyphenols are extracted from raspberries using various solvents and analysed using different histochemical methods to quantitatively and qualitatively evaluate their concentrations. The main polyphenols found in raspberries include ellagitannins (tannins), phenolic acids, anthocyanins (flavonoids), catechins (flavonoids), and proanthocyanidins (flavonoids) [12,16-18]. These polyphenols possess antioxidant, anticancer, anti-inflammatory, antimicrobial, antilipidemic properties, among others, which continue to be the focus of interest for researchers [54].

The characteristics of the extract obtained are determined by pre-extraction and extraction factors. The pre-extraction factor determines the amount of polyphenols in the berries, while the extraction factors govern the ability to extract those desired molecules from the berries [55]. The phytochemical content of raspberries depends on factors such as the geographical region and season of harvesting, which are controllable, while factors like climate, exposure to sunlight, water intake, and ripening stage during harvest cannot be controlled by the researcher [56]. These raspberry extracts are tested on animal study models and humans in clinical trials to assess their impact on human ailments [34,42,44]. The results of these studies instill hope for potential cures.

Plant extracts have been implicated in treating oral diseases in the field of dentistry. Turmeric, aloevera, yarrow, tea leaves, khat, orange, myrrh, wintergreen, St. John's wort, pepper-rosmarin, chamomile, tea tree, peppermint oil, antplant, propolis, mastic tree, rosemary, meswak, clove, myrobalan, red clover, winged prickly ash, and ginger are common plants and trees that have traditionally been utilised in various parts of the world to treat oral ailments. Similarly, raspberries have been experimented with to harness their properties in treating various oral diseases such as oral cancers, premalignant lesions, and oral microbial infections like candidiasis [46].

CONCLUSION(S)

Based on the available literature evidence, the various phytochemicals present in raspberries have been shown to possess multiple medically important properties. Further advancements in extracting and utilising these properties in the field of medicine are likely to attract the attention and curiosity of researchers, opening up new avenues for research.

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