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Prunus Avium L.; Phytochemistry, Nutritional and Pharmacological Review

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Abstract

Current studies were made to investigate the phytochemistry, nutritional and pharmacological studies on *Prunus Avium* L. (sweet cherry or wild cherry). The plant is a rich source of many phytochemicals, nutrients, phenolic compounds, sugars, anthocyanins, perillyl and phenolics. The presence of chemical compounds such as cyanidin 3-sophoroside, cyanidin 3-rutinoside, cyanidin 3-glucosylrutinoside, cyanidin 3-glucoside *etc.* renders the cherry fruit to demonstrate anti-cancer and anti-oxidation potential, antigenotoxic, anti-inflammatory, cytotoxic, antimicrobial, neuroprotective and diuretic activities. Cherry consists of cyanogenic glucoside (prunasin) which assists the body in tranquilizing cough and also effective for nervous touchiness and nervous dyspepsia. For secure treatment of cough, pharmaceutical companies isolate prussic acid from the cherry bark as a dynamic component. Wild cherry is also helpful in treatment of arthritis due to the presence of anthocyanins.

Introduction

Plants have been known as a traditional source of medicines since old ages due to their important pharmacological properties and therapeutic potential [1-3]. Their use in medicine will be continued in the coming future and as basic raw material for food industries, perfumes and cosmetics [4]. Natural products extracted from medicinal plants have played an excellent role in cancer treatment. Plant based anticancer agents include vincristine, and etoposide, topotecan and irinotecan, the camptothecin derivatives, vinblastine, taxol etc.; they have been clinically used throughout the world [5]. *Andrographis paniculate* is used for the detoxification of body and as a remedy for fever and cold [6]. *Psidium guajava* (guava) is highly effective in the treatment of caries, diabetes, hypertension, cough, swollen gums wounds, oral ulcers, gastroenteritis, dysentery and diarrhea and also to improve locomotors coordination. Its fruit is highly rich in vitamins C & A as well as minerals [7]. *Hippophae Rhamnoides Linn* is an excellent source of potent antioxidants and vitamins, carotenoids, flavonoids, phytosterols and lycopene. It possesses adaptogenic and anti-stress activity and can also be used to increase hypoxic tolerance in animals and to lower the level of stress hormones. The presence of many important ingredients in it gives healthy and beautiful look to the human body [8]. *Asparagus racemosus* was used traditionally for the treatment of issues related to female reproductive system and as a general health tonic. Its neuroprotective, hepatic, anticancer, antioxidant, antidiabetic, antimicrobial, antitussive, antiurolithiatic, aphrodisiac etc. [9].

Sweet cherry (*Prunus avium* L.) (Figure 1) is a commercial plant which belongs to the family Rosaceae. It is commonly known as wild cherry [10]. The *Prunus* (genus) shows drupes on fruits; this genus is divided into three major subgenera: amygdales (*Prunus persica* L.), prunophora apricot (*Prunus armeniaca* L.) and cerasus (sweet cherry, *Prunus avium* L.) [11]. These species require favorable growth conditions like low winter temperature and cold climate. Due to different heating and chilling conditions before flowering, there is variation in flower formation [12]. Anyhow, different studies on apricot, sweet cherry and peach revealed that chilling conditions have more significant effect on flowering time as compared to heating conditions [13]. Genotypes growing in low chilling conditions are more abundant due to their early growth in cold seasons and vulnerable for damage as compared to genotype in high chilling conditions. Improper chilling in warm regions produces bud breaks and irregular floral and fruit development [14]. However, there is still a need of

further studies to investigate the genetic makeup of flowering time, although there are some limitations behind biochemistry and physiology of the flowering process [15]. The plant is found in Pakistan (Quetta, Pishin, Ziarat, Kalat, Zhob, Mastung, Loralai, and Swat & Murree), Europe, Western Asia, and British Isles to Morocco & Tunisia, Northern Iran, Western Himalaya, USA, Russia, Italy, Turkey and Trondheim fjord region in Norway and Caucasus. Cherry seeds require exposure too cold for its germination. It finds applications in ornaments, dyes, timber, smoking foods, chewing gum, medicines, dyes [10,16].



Figure 1: Fruits on branches of sweet cherry plant.

Keeping in view the greater importance of sweet cherry, current studies were made to review its phytochemistry, nutritional and pharmacological potential.

Methods

Literature search strategy and selection criteria

Relevant literature was reviewed to overview the phytochemistry, nutritional and pharmacological potential of *Prunus Avium* L. (sweet cherry or wild cherry).

Discussions

Fruits of Cherry

Sweet cherry flowers vary according to pollen efficiency depending on the type of cultivar and rootstock [17]. Cherry being a non-climacteric fruit possesses different pattern and stages as compared to climacteric fruits such as potato. The development in cherry fruits is very rapid as compared to other fruits because it is an ovary derived fruit [18]. Fruit formation in sweet cherry terminates after 4 to 9 weeks [19]. However, it may also result in weakened fruit formation. Attack of fungal pathogens on weakened tissues is more frequent as compared to healthy tissues because moisture and nutrients uptake is more convenient for the germination

of spores and growth of mycelium. Infection formation is more common in weakened tissues [20]. There are earlier reports that weakened sweet cherry are easily attacked and infected by fungal pathogens which results in poor growth and bud breakage as compared to normal or healthy fruits. Healthy fruits are more resistive to diseases, infections and pathogens attack as compared to weakened fruits [14,21]. Synthetic fungicides are excellent source for protection of fruits from invaders and pathogens; one of these substances is salicylic acid which is used against virulent pathogens [18]. It is evaluated from various researches that exogenous pathogenic treatment would enhance the self-defense power against pathogens by the action of defense genes [22]. However, still very few data is available on the process of fruit ripening and response of pathogens against attack and infections especially at proteomic level [23].

After harvesting, fruits of sweet cherry are rapidly damaged and reach at demanding site with low quality. In order to avoid from this situation, pre-harvesting methodologies and cold storage areas are required and cherry fruits should be immediately transported and marketed [24]. Another method for quality improvement is the use of protective coatings like alginate natural polysaccharides against oxygen, carbon dioxide and water vapors [25]. For the identification, analysis and characterization of sweet cherry, different techniques can be applied like solid phase micro-extraction technique (for extraction of volatile compounds), linkage mapping, GC-O analysis to detect the peak area and retention time of aroma-active compounds, GC-MS analysis to draw the mass spectrum of different cherry derivatives, quantitative analysis, RNA analysis, anthocyanins analysis and statistical analysis to perform various tests e.g. ANOVA and Duncan's test. Protein analysis is performed to investigate the components of proteins in plants [26]. But it is still controversial to identify and develop the novel methods, new and cost reducing methodologies, latest techniques for the determination, analysis and elucidation of synthetic variations in aroma- active constituents [13].

Phytochemistry

Sweet cherry is a great source of many phytochemicals, nutrients, phenolic compounds, sugars and organic acids. The phytochemicals extracted from sweet cherry act as a secondary metabolite. It consists of anthocyanins, perillyl and phenolic compounds including cyanide-3-rutinoside and flavonol p-coumaroquinic acid having importance in anti-cancer and anti-oxidation activities [10]. Sweet cherry contains two main phytochemicals: anthocyanins-a phenolic

compound possessing disease fighting attributes and quercetin that is a very effective anti-oxidant and anti-carcinogenic *in vivo* as well as *in vitro* conditions [27]. Different diseases like lung cancer and coronary heart disease are reduced with the consumption of quercetin rich foods. Five mili grams (mg) of quercetin in each day proves very effective [28].

Sweet cherry consists of anthocyanins as major phenolic compounds. Cyanidin 3-glucoside, cyanidin 3-rutinoside, cyanidin 3-sophoroside, pelargonidin 3-glucoside, pelargonidin 3-rutinoside, peonidin 3-glucoside, and peonidin 3-rutinoside. The cyanidin 3-sophoroside, cyanidin 3-rutinoside, cyanidin 3-glucosylrutinoside, cyanidin 3-gucoside, cyanidin 3-arabinosylrutinoside, pelargonidin 3-glucoside and peonidin 3-rutinoside were reported in sour cherry. Along with hydroxycinnamates sour and sweet cherries also contain neochlorogenic acid, p-coumaroylquinic acid, flavonols and flavan-3-ols [11] (catechin, epicatechin, quercetin 3-glucoside, quercetin 3-glucoside, quercetin 3-rutinoside and kaempferol 3-rutinoside). At early phase of sweet cherry ascorbic acid, total antioxidant activity (TAA) and total phenolic compounds declines but enhances from ripening stage 8 corresponding with anthocyanin assemble, fruit darkening and effective in growth of human colon cancer cells inhibition. Phenolic compounds provide help in plant's defense, to neutralize reactive oxygen, for survival and prevention of molecular injury, and smash up by insects, herbivores and microorganism. Tannins plays major role as stimulants to damage pro-oxidants and toxins while its concentration changes with plant's genotype, environmental conditions and tissue developmental stage [29]. Figure 2 displays some important phytochemical constituents in sweet cherry cultivars derived from shikimic acid *via* various metabolic pathways.

Nutritional value

Sweet cherries are considered one of the most appreciated fruits throughout the world because of their pleasant taste and aroma [30]. Moreover, they are rich in several nutritional contents (sugars and organic acids) and phytochemical compounds including phenolics, melatonin, serotonin, carotenoids etc; all these contents are very important for biological functions [30,31]. It has been reported by many clinical studies that cherries and their derivatives have numerous beneficial effects on human health [32]. Their consumption owes positive effects on human health due to their wealthy and vast constitution. They can be applied in food and pharmaceutical formulations as they have the potential to prevent and/or ameliorate

oxidative-stress disorders and thus can diminish proinflammatory markers and free radical species [31]. The endemic sweet cherry cultivars (Della Recca and Del Monte) have shown good nutritional properties. Both the cherry cultivars have shown good quantities of macronutrients i.e., lipids, carbohydrates and proteins [33]. Sweet cherries are rich in important nutrients and are excellent sources of vitamin C, fiber, carotenoids, potassium, hydroxycinnamates, quercetin, melatonin and anthocyanins. However, the amounts of bioactive components and nutrients may be significantly changed depending upon the degree of ripeness, processing, postharvest storage conditions and UV concentration. So, the intake of cherry is associated with many health benefits and potential prevention against Alzheimer's disease, inflammatory diseases, diabetes, cardiovascular disease and cancer. Cherries exhibit excellent antioxidant potential, anti-carcinogenic effects, COX 1 and 2 enzyme inhibition and low glycemic response [27]. The rise of oxidative stress may lead to numerous human chronic inflammatory diseases. Cherries possess natural anti-inflammatory and anti-oxidant properties because they are a rich source of vitamin C and polyphenols [34].

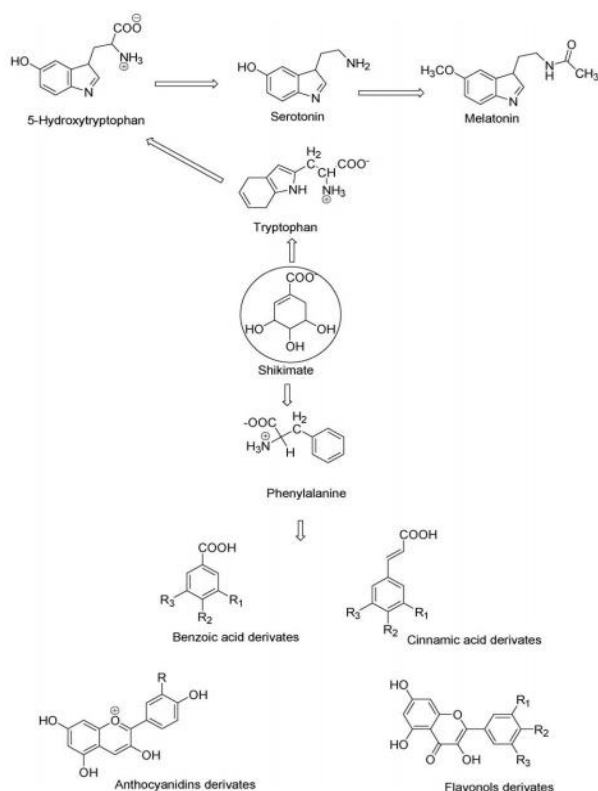


Figure 2: Some important phytochemical constituents in sweet cherry cultivars derived from shikimic acid *via* various metabolic pathways.

The consumption and production of sweet cherries has been increased continuously due to consumer

awareness of their health benefits. Their production has been increased from 1.9 to 2.32 million tons in the last 16 years; Iran, USA and Turkey are major producers. However, the production of source cherries (1.1–1.3 million tons) has been remained static during the same period. Sweet cherries are highly perishable and are often consumed fresh. They are appreciated for their organoleptic aspects including color, texture and taste. The sour cherries are mostly processed and are rich in bioactive contents. However, a lot of health benefits are associated with both kinds of cherries (sweet and sour); they enhance cognitive function, modulate blood glucose, reduce inflammation and counteract oxidative stress. The recovery of exercise-induced muscle damage has been reported by the supplementation of sour cherries [35]. It is important to select a suitable harvest period to ensure maximum functional, nutritional and organoleptic properties of fruits of sweet cherries. The softening process, accumulation of glucose and fructose and skin color of sweet cherries are associated at early developmental stages [36].

Sweet cherries are used as fresh fruits as compared to sour cherries which are used in synthetic foodstuff (freezing, canning and juices). According to studies, fresh cherries show health advantages on animal cells due to the presence of dietary phenolics thus protecting the cell-damage from oxidative stress [37]. However, it is important that even though the use of *Prunus* fruit is commonly safe, its barks, shoots, leaves and pits contain cyanogenic glycosides that may be poisonous and fatal for live stalk. Its seeds and young rapidly growing leaf tissue contain very high concentration of potential toxin [38]. The cyanide even becomes more concentrated in damaged and wilted leaves due to initial loss of water from leaves. However, cyanide level may be lowered due to evaporation of cyanides which have volatile nature [38,39]. Although pits and leaves of *Prunus* contain the highest concentrations, however, animals should also be kept away from the bark, branches, dormant buds, twigs *etc* [40]. After ingestion of a toxic plant material, the feeding animal will show distressed behavior and apprehension and then rapid/labored respiration, ataxia, severe weakness, gross muscle tremors, gross muscle tremors, staggering [41,42], attempts to urinate and kicking and titanic-type seizures. It will be then followed by very slow heart rate and slow/stop breathing. Finally, the animal may become comatose and eventually a period of brief paddling of the feet with convulsions may happen before death. However, the blood remains well-oxygenated and red so there will be no cyanosis (blue coloration due to deoxygenated blood) [40,41]. Depending upon the amount of dosage and the size of animal, these events will take place with 2-3 minutes or may prolong to 1 to 2 hours. However,

prognosis for recovery is usually favorable if the animal is survived up to first hour [41,42]. The sequence of events occurs very rapidly so treatment of cyanide intoxication is often late [41]. For treatment, cellular respiration should be unblocked. An antidote solution consisting of 3 g sodium thiosulfate and 1 g sodium nitrite in 50 mL of water may be administered intravenously for a sheep while the dosage may be increased to 15 g sodium thiosulfate and 5 g of sodium nitrite in 200 mL of water for cattle [41,42]. It may also be followed by an oral administration of glyceraldehyde, molasses or glucose. Cyanide poisoning may be prevented or its risk may be reduced in livestock by lowering the pH of stomach (by feed management and suitable supplements) since the stomach pH displays an important role in hydrolyzing the cyanogenic glycoside [41]. The rate of natural detoxification can be increased by using sulphur supplements in salt [41,42].

Pharmacological Potential

Cherries consist of cyanogenic glucoside (Prunasin) which assists the body in tranquilizing cough, reduces pain, cold, bronchitis, flu, tuberculosis and asthma. It is not only a gentle tranquilizer to treat cough but also effective for nervous touchiness and nervous dyspepsia [37]. For secure treatment of cough, pharmaceutical companies isolate prussic acid as a dynamic component from cherry bark [19]. In autumn, prunasin is accumulated for future use because the level of prunasin is high, and is transformed into lethal hydrocyanic acid in digestive region while its small amount stimulates respiration and improves digestion [15]. Many beneficial effects have been reported on to the health by consumption of sweet cherries; they include prevention and modulatory effects in numerous chronic diseases e.g., inflammatory diseases, cancer, diabetes mellitus and cardiovascular issues [43]. The consumption of vegetables and fruits in diet is linked with lowering of incidences of degenerative diseases including cancer and cardiovascular diseases. The presence of several polyphenols and antioxidants are present in sweet and sour cherries renders antioxidant, anti-inflammation properties and anticancer properties to sweet cherries [44]. An overview of 29 human studies (literature) shows that cherries consumption have improved sleep in 4/4 studies, arthritis in 5/5; blood pressure in 5/7; exercise-induced muscle soreness and loss of strength in 8/9; inflammation in 11/16 and decreased markers for oxidative stress in 8/10 studies [34].

Antigenotoxic Activity

The inhibitory effects of several fruits on 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) genotoxicity were

evaluated. The highest inhibitory effect (IC₅₀)=0.17%) was displayed by sweet cherry juice followed by juices of blueberry, plum and kivi fruit (IC₅₀)=0.48-0.71%). Moderate inhibition is shown by juices of watermelon, black-berry, strawberry, black currant and red delicious apple while weakly active juices include sour cherry, grapefruit, red currant and pineapple [37,45].

Diuretic Activity

Studies were made to evaluate the diuretic activity of cherry fruit extracts on rats. The results have shown that cherry fruit extracts are effective in the treatment of various chronic diseases. The application of these extracts has shown the diuretic, membrane-stabilizing and hypourisosemic effects in rats as water reabsorption was suppressed while kidney filtration was improved with increase of excretion of creatinine and uric acid from body. Also, the degree of hemolysis of red blood cells and damage to erythrocyte membrane was prevented [46]. Hooman *et al.*, 2009 studied the diuretic activity of sweet cherry stalk powder on 13 healthy volunteers. Oral administration of 2.0 g (as capsule) dose per person has increased the mean urine volume as well as excretion of calcium, sodium and chloride through urine but the amount of urine osmolality and urine potassium did not change. Sodium chloride excretion was increased up to 15% which might be comparable to loop diuretics, thiazides, osmotics or carbonic anhydrase inhibitors. The results were same in both the males and females. It was concluded that cherry stalks can be used as a mild diuretic agent for therapeutic purposes without any adverse effects. Cherry stalks were traditionally used in Iran to treat renal stones. However, it should be used with care in patients having disorders associated with the deficiency of sodium or/and chloride and calcium since its administration results in excessive section of these elements through urine [47].

Anticancer Activity

It has been investigated that sweet cherry extracts (EAAEC & EEC) possess good anticancer potential against human breast cancer cell line MCF-7 as indicated by in-vitro studies using MTT assay. The extracts have shown excellent potential to inhibit the cancer cells when compared with standard drug doxorubicin. Maximum cell growth inhibition (92.90%) was found observed with 10 µg (IC₅₀ = 2.4 µg/ml) of EEC while it was found to be 92.49% with 10 µg (IC₅₀ = 2.9 µg/ml) of EAAEC [48].

The cytoprotective effects of sweet cherries have been extended in the last few years to the metabolic reprogramming of cancer cells, invasion and migration

and the regulation of cell death and proliferation. It is quite exciting to demonstrate the broad action of sweet cherries over several hallmarks of cancer. Thus there are possibilities of using this fruit as a coadjuvant therapy in cancer treatment as a dietary supplement [30]

Antioxidation Activity

Antioxidant potential of numerous parts of the plants are commonly reported [49-51]. Many human chronic inflammatory diseases are associated with increased oxidative stress [34]. There are reports that endothelial cells can be protected from oxidative stress by natural polyphenols-rich sweet cherry extracts [32]. The presence of numerous phenolic compounds renders antioxidant potential to *Prunus avium* L. (sweet cherries) [52]. Sweet cherry extracts are highly rich in phenolic compounds, with anthocyanins as the main bioactive compounds [30]. Studies have shown the presence of polyphenolic contents, total tannins, total flavonoids and total anthocyanins in the ranges of 4.12-8.34, 0.19-1.95, 0.42-1.56 and 0.35-0.69 mg gallic acid equivalents/g dry fruit weight, respectively. Although significant amounts of phenolic compounds are present in sweet cherry fruits, their antioxidant potential is not related only with the total anthocyanins, flavonoids or polyphenolics [52]. The quantity of bioactive compounds depends upon the plant parts (e.g., leaves, petioles, fruits) of the sweet cherry. Thus, petioles and leaves of sweet cherry contain a higher concentration of polyphenols, carotenoids, vitamin C and dietary fiber and also the greater antioxidant activity than the fruits; however, anthocyanins are present only in fruits. The polyphenols include myricetin, p-coumaric acid, chlorogenic acid and coffee acid. Leaves also contain ferulic acid. The identified myricetin and phenolic acids are considered as strong antioxidant and anti-inflammatory agents. Due to high antioxidants level, leaves and petioles can be used to produce new functional food e.g., drinks and food additives (as lyophilized extracts or powders). The leaves and petioles are effective for the treatment of many diseases including cancer, obesity, diabetes and cardiovascular diseases. However, further investigations are required to apply the plant material in food industry [53].

Anti-inflammatory Activity

Anti-inflammatory potential may be associated with the presence of several antioxidants in sweet cherries [54]. Anthocyanins from cherries have potential anti-inflammatory and anti-oxidative effects on Freund's adjuvant-induced arthritis (AIA) [55]. Cherry fruit extracts have been reported to be as efficient as the commonly used anti-inflammatory synthetic drug dexamethasone. The use of cherry extracts by their

encapsulation in nanosystems based on chitosan derivatives represents an innovative and good strategy for delivering the polyphenols from cherry extracts. In this way, the intestinal absorption of cherry polyphenols is improved with the consequent increase of the anti-inflammatory and antioxidant potential. If higher polyphenol concentrations are required, PLGA-based nanosystems may be used as valid alternatives. Recently, complex systems based on nanoparticles have been investigated to improve the stability of phytochemicals and thus preserve the therapeutic potential of the encapsulated bioactive compounds. Although the fresh cherry fruit is a seasonal fruit, the use of cherry extracts with nanosystems prevents their degradation in gastrointestinal tract, thus cherry consumption and its benefits are not limited to seasonality [32]. The cyanidin from cherries is highly effective against the paws swelling in adjuvant induced arthritis (AA) in SD rats and is an excellent candidate for alleviation of arthritis [56].

Antimicrobial Activity

Sweet cherry extracts (SCE) have been reported to display antimicrobial activity against a wide spectrum of bacteria (gram-positive and gram-negative) as well as fungi [54]. For evaluation of antimicrobial potential, SCE were applied in the form of methanol-extracted pomace (mPOM), ddH₂O-extracted pomace (dPOM), methanol extracted juice (MEJ) and whole juice extracts (WJE). Mueller-Hinton agar was used to grow fungi/bacterial suitable for disk-diffusion method. WJE have displayed significant inhibition of *Proteus vulgaris*, *Escherichia coli* and *Enterococcus* Group D, and minor activity against *Streptococcus* Group B and *C. albicans*. On the other hand, MEJ exhibited minor attenuation of *Klebsiella pneumoniae* and *Streptococcus* Group A and higher activity against *P. vulgaris*, *E. coli* ESBL, *E. coli*, *Citrobacter koseri*, *Enterococcus* Group D and *Bacillus subtilis*. dPOM showed no activity against any gram-positive bacterium but it showed significant inhibition of *E. coli* ESBL, *E. coli* and *Enterobacter cloacae* and minor activity against *P. vulgaris* and *C. koseri*. mPOM displayed substantial inhibition of *B. subtilis* and *Enterococcus* Group D, with minor activity against *Streptococcus* Group B; it showed significant inhibition of *P. vulgaris*, *C. koseri*, *E. coli* ESBL and *E. coli*. These results demonstrate the effectiveness of sweet cherry extracts against a wide range of pathogenic bacteria and their corresponding applications in the medical field [17].

Neuroprotective Activity

Ethanollic extracts of *Prunus avium* were applied to evaluate the anti-amnesic and neuroprotective activity

against streptozotocin (STZ) induced neurotoxicity in mice. The ethanolic extracts have shown cognitive improvement which indicates its neuroprotective activity. However, there is a need of more studies to evaluate the isolated bioactive *Prunus avium* fruits for identification of molecular mechanisms involved in modulation of cholinergic transmission.

Conclusions

Sweet cherry (*Prunus Avium* L.) is a great source of many phytochemicals, nutrients, phenolic compounds, sugars, anthocyanins, perillyl. The chemical compounds such as cyanidin 3-sophoroside, cyanidin 3-rutinoside, cyanidin 3-glucosylrutinoside, cyanidin 3-glucoside etc enable the cherry to demonstrate anti-cancer and anti-oxidation potential, antigenotoxic, anti-inflammatory, cytotoxic, antimicrobial, neuroprotective and diuretic activities. Cherry is not only a gentle tranquilizer to treat cough but also effective to treat nervous touchiness and nervous dyspepsia. For secure treatment of cough, pharmaceutical companies isolate prussic acid from cherry bark as dynamic component. Wild cherry is also helpful in treatment of arthritis due to the presence of anthocyanins. The non-healthy and weakened fruits of cherry are more easily attacked by fungal pathogens as compared to normal or healthy fruits.

Competing Interests

None.

Author Contributions

All authors contributed equally.

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