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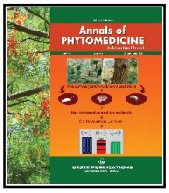

Invited Article: Open Access

Fruits that heal: Biomolecules and novel therapeutic agents

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Abstract

The advances in phytochemistry with bioactive components of fruits extended a preeminent new chemical entity endowed with various pharmacological effects. The bioactive components and the raw fruit components in any forms such as formulated, juice or in extracts were consumed and administered for therapeutic benefits, health and wellbeing of humans. Various fruits or their secondary metabolites (extract form) in Indian traditional medicine were used to treat or alleviate the symptoms of disease. They are used as anti-inflammatory, anticancer, antiulcer, cardioprotective, antianxiety, gastroprotective, nephro-protective, neuroprotective, antibacterial, antiobesity, antidiabetic and as supplement for rejuvenation. This article summarizes the recent pharmacological research and the medicinal value of fruits as well as their secondary metabolites for treating various ailments.

1. Introduction

A healthy diet and nutrition promote the health and wellbeing of human life and other living beings. Fruits and vegetables play a key role in human health and imparts the defensive ability to the human body against various diseases. Diet is one of the modifiable factors for the prevention of disease when imparted with the natural products such as fruits. Chronic disease of non-communicable disease (NCDs) such as obesity, diabetes mellitus, ischemic heart disease, genitourinary diseases, inflammatory disease, neurodegenerative disease and bone-related disease is highly intervenable by regular dietary modifications with fruits (Boeing *et al*., 2012). Promoting healthy lifestyle with nutritious diets comprising at least 400 g of fruits and vegetables improve the human health and rejuvenates the human system (Amine *et al*., 2003). It is predicted that overall, 2.7 million lives may be protected upon fruits and vegetables consumption. Fruits such as citrus, grape, blueberry, pomegranate, mango, orange, pine apple, strawberry, sweet cherry, lychee, apple, hawthorn and avocado have been extensively evaluated and have shown preeminent antioxidant properties which are beneficial for the therapeutic effect in alleviating various disease conditions. The major components of fruits constitute phenolic acids, phenolic polymers, coumarins, lignans, flavonoids, stilbenes, iso-flavonoids, anthocyanins, vitamins and trace elements. In general, polyphenolics are the compounds possess pharmacotherapeutic properties against various diseases (Costa *et al*., 2017). This article focussed on six Indian fruits for their therapeutic properties.

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2. Fruits and their healing properties

2.1 *Citrus limon* L. Burm. f. and citrus fruits

Citrus limon L. Burm. f. is commonly called as lemon fruit and belongs to the family Rutaceae. Lemon or citrus is one of the important fruits which is very commonly used in India and Southeast Asian countries and traditional medicine and as flavoured rejuvenating drink. Other citrus fruits found in India were *Citrus limetta*, *Citrus sinensis*, *Citrus medica* and *Citrus indica*. The common lemon fruit, *C. limon*, orange and mandarin were widely used by mankind. Flavonoids, vitamins, dietary fibres, minerals, carotenoids and essential oils were the natural compounds were present in the lemon (González-Molina *et al*., 2010). Their health-promoting effects and properties have been associated with their contents; namely, vitamin C and flavonoids, due to their natural antioxidant characteristics. Overall, lemon fruits, rich in flavonoids, are a very important part of a balanced diet, particularly for their role in prevention of diseases, such as obesity, diabetes bloods lipid-lowering, cardiovascular diseases, and certain types of cancer.

Figure 1 a

Figure 1 b

Figure 1 a and b: Citrus fruits *(C. limon and C. sinensis).*

2.1.1 Major phytotherapeutic and antioxidant compounds

Vitamin C is highly enriched in lemon and contains coumarins, limonoids, phenolicacids, carotenoids and essential oils. Mostly the other secondary metabolites such as flavonoids are present in the fruits and approximately sixty were found in citrus fruits. In lemons and grape fruit juices, myricetin and rutin were commonly identified. The peel consists of pectin, kaempferol, iso/limocitrol 3-β-glucoside, limocitrol and quercetin were found in peel.Naringin is also called as neohesperidoside, narirutin (rutinoside) and hesperidin (rutinoside) are commonly present in major quantities. Other minor compounds were hydroxycinnamic acids and its derivatives (chlorogenic acid, caffeic, ferulic, p-coumaric acids and sinapic) were present. Trace elements such as selenium (one of the important factors for antioxidant property), copper, zinc and iron were present (González-Molina *et al*., 2010).

2.1.2 Pharmacotherapeutic effects

Lime juice and the secondary metabolites present in the citrus fruits were reported to have various therapeutic effects. The essential oils and β-limonene and β-pinene were extracted from the ethanolic extracts and found to possess the gastroprotective mechanism. It protected the ethanol-induced and indomethacin induced ulcer. In this study, it was found that there was a significant improvement in increased mucous, prostaglandins and increased the vasoactive intestinal peptide to reduce the acid intake (Harsha *et al*., 2017). Vitamin C in the citrus fruits exhibits antioxidant capacity and value adds the health benefits in reducing the risk of cardiovascular and ischemic heart disease (Diplock, 1994). The flavonoids present in the citrus fruits exhibits antiproliferative effect and also reported to possess modulatory effect in tyrosine kinases (Camarda *et al*., 2007). The components such as eriocitrin and hesperetin of citrus fruits exhibits lipid lowering effect in diet induced hypercholesteraemic rats and also prevented the low density lipoprotein (LDL) oxidation, prevented the atherosclerotic plaque formation to reduce the cardiovascular risks (Lv *et al*., 2015). Hesperidin possess cardiovascular remodelling by inhibiting tumour necrosis factor receptor type 1 (TNF α1) and expression of matrix metalloproteinase-2 and 9 (MMP-2 and 9) (Maneesai *et al*., 2018). Lemon juice is having antibacterial property against diarrhoeal pathogen (Ekawati and Darmanto, 2019). The components like hesperidin and naringenin have effects on cytochrome P450, as well as P450 3A4 (CYP3A4) and they cause drug interactions with medicines. Hesperidin improved the learning and memory in aluminium chloride at 100 mg/kg (60 days) neurotoxicity induced rats and reduced the acetylcholinesterase (AChE) in rat cortex and hippocampus (Thenmozhi *et al*., 2015). Hesperetin (40 mg/kg b.w) in streptozotocin (STZ) induced diabetic rats improved from diabetes and controlled the lipid levels (Jayaraman *et al*., 2018). Naringenin and hesperetin increased the glutathione peroxidase (GPx), glutathione reductase (GR) superoxide dismutase (SOD); indicating the potential antioxidant property (Miler *et al*., 2016). In aromatherapy, the citrus essential oils and their compounds are used as rejuvenating agent to improve the behavioural and psychological symptoms of dementia and psychosis (González-Molina *et al*., 2010).

2.2 *Carica papaya* L.

Carica papaya L. 'Calina' is highly edible and is well known for its nutritional value with carbohydrates and sugars.The plant is distributed widely in tropical regions and belongs to the family Caricaceae. Ethnopharmacologically, the papaya fruit is used by southeast Asian for various health benefits such as antioxidants, anti-inflammatory, neuroprotective, recovery and rejuvenation after pregnancy, mensural disorders and also uterine cancer (Kong *et al*., 2021).

Figure 2: C. *papaya*.

2.2.1 Major phytotherapeutic and antioxidant compounds

The nutritional components are sugars, Ca_2^+, proteins, vitamins, secondary metabolites and volatile compounds. The secondary metabolites include flavonoids. Polyphenols and tannins and are having health promoting properties. The fruits are enriched with carotenoids, vitamin A, vitamin C, vitamin B-6, vitamin K, thiamine, riboflavin, niacin, lycopene, zetacarotene, beta-crytoxanthin and betacarotene -5- 6- epoxide (Nwofia *et al*., 2012). The unripe fruits also contain the proteolytic enzymes such as papain and chymopapain.

2.2.2 Pharmacotherapeutic effects

The papaya fruit is traditionally used for human health and wellbeing. Generally, it was used for boosting the immunity, skin diseases, digestion, abortifacient, anti-inflammatory and rejuvenation (de Oliveira and Vitória, 2011). The ethanolic fruit pulp extract was studied in mice for anxiolytic property and found that 100 mg/kg treatment exhibited the anxiolytic property (Kebebew and Shibeshi, 2013). Fermented fruit extracts were supplemented in Alzheimer's patient (AD) and found to have antioxidant actions, indicating that it is useful to control the age related dementia and associated neurodegeneration (Barbagallo *et al*., 2015). It is also effective against hypothyroidism (Tomella *et al*., 2014). Green and ripe fruits epicarp extract were administered in mice and found having good wound healing property (Anuar *et al*., 2008).

The liver cellular integrity and oxidative damage in hepatocytes is protected by the fruit extract in N-methyl-nitrosourea induced hepatocellular carcinoma in balb/c mice (Somanah *et al*., 2016). Clinical studies indicated that the consumption of 6 g fermented papaya product for 14 weeks reduced the haemolysis and protein accumulation in prediabetics individuals' plasma. It is also reaveled that consumption of fermented fruit extract on a daily basis improved the antioxidant defence system (Somanah *et al*., 2016). It is also stated that the fruit extracts were effective against stroke and exhibts neuroprotective effects (Mahomoodally and Mooroteea, 2021).

2.3 *Phyllanthus emblica* L.

The fruits of *Phyllanthus emblica* L. (*Emblica officinalis*) has been broadly used as a tonic for its therapeutic potential. It belongs to the family, Phyllanthaceae and is called Indian gooseberry. It is used in Indian system of traditional medicine such as Ayurveda, Siddha and Unani including Chinese medicine to treat various illnesses. It was one of the major ingredients in "Triphala" formulation in Indian traditional medicine system. It is used for the treatment of diarrhoea, inflammation, hemorrhoids, diabetes, liver enlargement and as neurotonic immunostimulant, digestive as well as carminative (Saini *et al*., 2022).

2.3.1 Major phytotherapeutic and antioxidant compounds

The main composition of emblica is emblicanin A and B, phyllemblin, gallic acid, corilagin, furosin and geranin. The fruit juice has high content of vitamin C. It also has sugars such as D galactose and fructose. The amino acids present in the emblica fruit is glutamic acid, cysteine, lysine and aspartic acid. Vitamin E, thiamine, nicotinic acid, riboflavin are the other components found. The micro and macronutrients elemental components such as sodium, potassium, iron, magnesium, zinc and selenium are present. It also contains fixed oils such as linoleic, oleic and palmitic acid.

Figure 3: Fruits of *P. emblica*.

2.3.2 Pharmacotherapeutic effects

The fruit extracts at 100 and 200 mg/kg were treated in Swiss albino mice and found to possess immunomodulatory effect. It increased the antibody titre of hemagglutination and lymphocyte distribution. Ethanolic extracts of embilca at 500 mg/kg reduced the yeast induced pyrexia in rats and exhibited anti-inflammatory effect in carrageenan induced paw oedema (Perianayagam *et al*., 2004). It is also exhibited the anti-inflammatory effect by reducing the leukotrienes (LTB4) and thromboxane B2 (TXB2). Phyllaemblicin B and C, corilagin and elaeocarpusin were evaluated in cell lines and found to posses antiproliferative effect. The antidiabetic effect was evaluated by preclinical and clinical studies. Treatment of 1-3 g of fruit powder in the healthy volunteers controlled the blood sugar, cholesterol and triglyceride levels. It is also protected the impairment in antioxidant defence system. The antidiabetic effects were also studied in STZ induced rats and found to control blood sugar and all the pathological changes during diabetes. Flavonoids of emblica fruit exhibited its potential effects on hypolipidemic in nonalcoholic steatohepatitis (Perianayagam *et al*., 2004; Somanah *et al*., 2016, 2014). The fruit powder also reduced the diabetic neural and vascular problems during diabetic conditions. It is also inhibited the tumour necrosis factor-α (TNF-α) and interleukin -1 (IL-1). In adipocytes cells, the extract exhibited the expression of PPAR-γ to control the diabetic conditions. Furthermore, the emblica extracts exhibit good antimicrobial effect against various organisms. The neuroprotective effect is well exhibited by inhibition of AChE and improved the learning and memory in rodents. 100 mg/kg treatment for 60 days decreased the aluminium chloride induced neurotoxicity and reduced the oxidative stress in brain. The fruit extract also exhibited protective effect against epilepsy in animal models and have wide pharmacotherapeutic effects in managing and treatment of various ailments (Saini *et al*., 2022).

2.4 *Punica granatum* L.

Punica granatum L. belongs to the family, Punicaceae and the fruits were commonly called as pomegranate. It is a functional food and has 57% as edible part with juice accounts for more than 36%. In tradition Indian system of medicine, it is used as health prosperity and fertility aid. The major components are amino acids, sugars, minerals, flavonoids and other phenolic compounds (Ge *et al*., 2021).

The medicinal property is found in its parts such as fruits, peel and seeds. It has an extensive variety of pharmacological effects such as anti-inflammatory, antibacterial, antioxidant and antiviral properties. It is also used as immunomodulatory and in the management of diseases such as atherosclerosis, diabetes, blood pressure, obesity, cholesterol, cancer and ulcers (Sudheesh *et al*., 2018).

Figure 4: Fruits of *P. granatum*.

2.4.1 Major phytotherapeutic and antioxidant compounds

Pomegranate juice consists of citric acid, quercetin and anthocyanins (delphinidin andpelargonidin and cyanidin). It is also enriched with vitamins (C, A and E). Apart from these components, the juice consists of carboxylic acids, rutin, apigenin, catechin, and proanthocyanidins. The fruit peel consists of anthocyanins, flavonoids and flavonols. It is also contains ellagic acid derivative and their glycosides. The tannin components were lignin, punicalagins and paeoniflorin punicalins. It was also identified that primary alkaloids such as pyrrolidine and piperidine were present (Ge *et al*., 2021).

2.4.2 Pharmacotherapeutic effects

The pomegranate juice is highly antioxidant and improves the plasma antioxidant markers (Sudheesh *et al*., 2018). The components delphinidin, pelargonidin, cyanidin possess highly antioxidant value (Ge *et al*., 2021). Pomegranate peel extract exhibited broad spectrum of antibacterial activities in *in vitro* studies. Antiestrogenic effect of pomegranate juice is established in cell lines for oestrogen positive and oestrogen negative breast cancer (Vini *et al*., 2016). The juice exhibited antiprostrate effects in clinical studies (Thomas *et al*., 2014). In clinical studies, the patients treated with the juice indicated good antihypertensive effect by inhibiting the angiotensin converting enzyme. The long-term administration of pomegranate juice regulated the blood pressure and reduce the common carotid intima media thickness (Asgary *et al*., 2016). In rats, the juice exhibited ACE inhibition and reduced the systolic blood pressure. Antihyperlipidemic effect was reported in pomegranate peel extracts by regulation the HDL-C. In high fat fed rats, the lipid parameters (cholesterol and triglycerides) were regulated, exhibited anti-atherosclerotic and antiobesity effects. The pomegranate juice also has the potential effect on treating cerebrovascular disease. It inhibits cyclooxygenase-2 and inducible nitric oxide and exhibits anti-inflammatory actions. It also reduces the production of interleukin (IL). It also exhibits immunomodulatory effect. In neurodegenerative disease condition, treatment with the fruit juice improved learning and memory. The anthocyanin of pomegranate juice inhibits the AD type of neurodegeneration and dementia (Essa *et al*., 2015) by reducing the beta amyloid fibrils. Pomegranate components also regulate the MAPK pathway and NFKB pathway to inhibit the tumour growth. Pomegranate products also exhibits the PPAR-γ activation and regulates the glucose levels. Apart form all these effects, the juice protects the hypoxic ischemic damages in new born mice exhibits neuroprotective effect in various neurodegenerative conditions (Ge *et al*., 2021).

2.5 *Mangifera indica* L.

Mangifera indica L. is extensively available in India, affordable economically and very commonly found. It belongs to the family Anacardiaceae. It has high nutritional value and majour health benefits. The fruits are enriched with sugars, antioxidant components and fibres. Indian mango pulp and seed were used for the therapeutic property. Traditionally, mango seed powder is used for various ailments and fruits were used for their nutritional value (Maldonado-Celis *et al*., 2019). Ripe and unripe mango fruit was commonly consumed by Indian population. *M. indica* is widely cultivated in India and well distributed in Southeastern region and originated from the regions of India, Myanmar and Bangladesh (Kuhn *et al*., 2017).

2.5.1 Major phytotherapeutic and antioxidant compounds

The nutritional components in the mango are carbohydrates, proteins, lipids, fatty acids and amino acids as macronutrients and vitamins and minerals as micronutrients. The fruits contain polyphenolic compounds, pigments, volatile components, pectin and cellulose. The amino acids present in the fruits were cysteine, lysine, arginine, leucine, valine, phenylalanine and methionine. Omega-3 and omega-6 fatty acids are also enriched in the mango fruit. The fruit pulp consists of phenolic acids such as hydroxybenzoic and hydroxycinnamic acid derivatives. The hydroxybenzoic acids in mango pulp are vanillic, gallic and syringic acid. There were three procyanidin components was identified in mango with seven phenolic acid derivatives. The xanthone derivatives of mango fruits were mangiferin, mangiferin gallate and homomangiferin. Quercetin, carotenoids and xanthophylls (antheraxanthin, neoxanthin, lutein, violaxanthin, auroxanthin and zeaxanthin) are found in fruit pulp (Maldonado-Celis *et al*., 2019).

Figure 5: *M. indica*.

2.5.2 Pharmacotherapeutic effects

The fruit pulp and the seed extracts of *M. indica* was widely used

as rejuvenating agent. In various studies of *in vivo* and *in vitro*, the potential effects such as anti-inflammatory, antioxidant, immunomodulatory, anticancer and neuroprotective activities have been well established. The current pharmacotherapeutic targets and research focused in the components of Mangifera. The anti-inflammatory and anticancer activities are exhibited by the inhibition of TNF-alpha and IL-1 (Mei *et al*., 2021). It also inhibits the toll like receptors (TLR-2 and 4). Mangiferin 5 mg to 400 mg/kg possessed various anti-inflammatory effect. In rats treatment of mangiferin reduced the high fat diet-STZ induced cardiomyopathy and doxyrubicin induced cardiotoxicity (Mei *et al*., 2021). Mangiferin is evaluated in mice and found to possess nuclear factor erythroid z-related factor (NRf2) transcription for cardioprotection (Song *et al*., 2020). It also alleviate the hypertension induced by uremic models in rats treated with 30, 60 and 120 mg/kg (Yang *et al*., 2018). Mangiferin also exhibits protective effects in mice in gestational diabetes mellitus and ameliorates the insulin resistance. In 100 mg/kg dose, it attenuated the brain injury through inhibiting the NOD-like receptor protein 3 (NLRP3) inhibition in rats (LEI *et al*., 2021). In adjuvant induced arthritis, 2 mg/kg mangiferin treatment inhibited the arthritis and is thought to mediate the regulation of mitogen activated protein kinases/nuclear factor kappa B (MAPK/NF-κB) pathways (Wang *et al*., 2021). Mangiferin treatment (10, 20 and 40 mg/kg) in scopolamine induced mice regulated the cholinergic neuro-transmission by increasing the acetylcholine and blocking the AChE enzyme. It increased the brain derived neurotropic factor, and neurotransmitter such as dopamine and noradrenaline (Walia *et al*., 2021).

2.6 *Fragaria ananassa* (strawberry) Duchesne

The common name of *Fragaria ananassa* Duchesne (is strawberry and is cultivated worldwide. Strawberry belongs to the family Rosaceae. The fruits are aromatic, bright red juicy and sweet. Strawberries are a good source of anthocyanins, flavonoids, sugars and polyphenols with several micronutrients (Padmanabhan *et al*., 2015). The anthocyanins and polyphenolics in the strawberry is highly antioxidants and treat various diseases. The strawberry fruits are extensively used as rejuvenating agent, canned drinks, ice creams, chocolates and milk shakes.

Figure 6 a

Figure 6 b

Figure 6: The fruits of strawberry in plant and freshly plugged fruits of strawberry.

2.6.1 Major phytotherapeutic and antioxidant compounds

The major phytotherapeutic components in the strawberry are anthocyanins. They are flavonoid compounds. The anthocyanidins such as cyanidin, malvidin, delhinidin, peonidin, pelargonidin and petunidin are found. Ellagitannins, gallotannins, fisetin, quercetin, kaempferol, vitamins and amino acids were present. Fisetin is one of the major compound possessing good antioxidant effect and pharmacological activities (Giampieri *et al.*, 2012).

2.6.2 Pharmacotherapeutic effects

Strawberry has been studied for biological activity in *in vitro* and *in vivo* (preclinical and clinical studies). Strawberries consumption reduces the risk of cardiovascular disease, neurodegenerative disease, endocrine disease (diabetes and metabolic syndrome/obesity), cancer, prevents hypercholesterolemia, inflammation and oxidative stress (Giampieri *et al*., 2012). Other pharmacological activities include various researches in strawberry. In male mice, the strawberry homogenate at 40% with combination of other antioxidants exhibited the antiobesity effect (Quitete *et al*., 2021). In human trial 2, cups of strawberry juice administration reduced the atherosclerotic marks (Basu *et al*., 2010). In lipopolysaccharide induced inflammation, it exhibited the anti-inflammatory effects by inhibiting NFκ-B and stmulating the NRf2 pathways (Gasparrini *et al*., 2017). It also possess protective effect on ulcer by inhibiting IL-8. *In vitro* studies in the phenolic compounds of strawberry revealed the anti-cytogenetic damage. In diabetic mice, the administration of strawberry at a dose of 2.3% in food markedly changed the gut microbiome activity. In LPS induced stress in raw 264.7 macrophages, the strawberry extract treatment reduced the lipid peroxidation and enhanced the protection against DNA damage. Strawberry enriched diet (15%) protected the cardiotoxicity produced by doxorubicin in rats (Giampieri *et al*., 2016). Fisetin is a major component in strawberry and extensively exhibiting various protective effects in human health. It reduces the cardiotoxicity and ischemia in rats at the dose of 10 mg to 40 mg/kg. Fisetin also have various pharmacotherapeutic effects such as antidiabetic, anti-inflammatory, anticancer, hepatoprotective, neuroprotective and hypolipidemic (Khan *et al*., 2013). Fisetin treatment with 15 mg/kg for 6 weeks in aged rats condensed the AChE enzyme, enhanced

the antioxidants and Na^{2+}/K^{+}ATPase as well as calcium ATPase. (Zhang *et al*., 2018). It enhanced the autophagy gene expression of (Atg-3 and Beclin-1), sirtuin-1 and condensed the inflammation exhibited by the reduced cytokine cascade (IL-1β and TNF-α) (Yang *et al*., 2019). The potential to inhibit the diabetes, cardiovascular disease, inflammation, cancer and neuroinflammation are the preeminent effects of fisetin.

3. Conclusion

Scientifically, the fruits which were commonly used in India have a huge potential of alleviating various diseases. Mostly, the active components of the fruits were sugars, carbohydrates, proteins, amino acids, flavonoids, polyphenols, vitamins, minerals, steroids, alkaloids, and terpenes. Morden approaches of the medicine identifies the isolated molecules' function in treating various diseases. Despite of potential benefits, the consumption of fruits during allopathic medicine should be ratified to avoid any adverse effects such as hyperglycemia, enzyme induction and inhibition, *etc*. Other fruits are grapes, vaccinium, blueberry and lychee also have nutritious value and therapeutic potentials. However, regular intake of the fruits along diet protects the human system from ill health and rejuvenates, thereby the longevity of human life is promoted healthy. In conclusion, dietary consumption of nutrition and therapeutic phytocomponents enriched fruits reduces the incidence of disease.

Conflict of interest

The author declares no conflicts of interest relevant to this article.

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