Review Article

CITRUS FRUIT AS A POTENTIAL SOURCE OF PHYTOCHEMICAL, ANTIOXIDANT AND PHARMACOLOGICAL INGREDIENTS

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Abstract: *Plants are natural source of valuable products for benefits of human health. It is important source of phytochemical compounds having antioxidant, antimicrobial properties which may be applicable in different therapeutic applications. The plants of Citrus belongs to Rutaceae family, the most common plants of this family are orange, lime, mandarin, sour orange, lemon and grapefruit having numerous beneficial nutrients consumed by human beings. The citrus fruits have various pharmacological properties and its constituents are broadly utilized for many clinical applications. Conventionally these fruits have been extensively used in the treatment of the several disorders such as diabetes, scurvy, urinary disorder, indigestion and constipation, ulcers and also applicable for improvement of immune system. In this review, comprehensive study focused on some phytochemical compounds and the pharmacological activities present in some citrus fruits and its peel, which is has discarded as waste has been focused.*

Keywords: *Citrus, Sweet orange, Phenolic compounds, Flavonoids, Antioxidants, Vitamin-C*

1. INTRODUCTION:

Plant producing vegetables and fruits existing on the earth surface, since immemorial time and human beings obtains medicines from this plant. The human beings uses the medicines obtained from plant to treat various kinds of diseases and remove pain. Not only are human beings, animals also get benefit from them in different ways. According to a report of World Health Organization (WHO), approximately 80% of the world population still depends on herbal plant as a source of medicine for the treatment of different kind of diseases due to little side effects, easily availability and also due to low cost [1]. Plants contain various chemical compounds such as secondary metabolites having lots of biochemical and bioactivity properties which are applicable in various cosmetic and pharmaceuticals Industries also [2, 3, 4]. According to a survey more than 9000 plants have been marked for their therapeutic and medicinal properties [5].

Citrus fruit is one of the most valuable fruit crop grown in the world with a production rate of 89 million tons in year 2014 [6]. The genus Citrus carries numerous beneficial fruits which is grown worldwide due to their nutritional and medicinal importance [7]. Citrus belongs to the family Rutaceae, it is one of the largest families within order Sapindales. There are different species of Citrus fruit (Table 1) which is present in India and worldwide are being used for multipurpose.

One of the important citrus fruit is sweet lime (*Citrus limettarisso*), commonly known as "Mosambi" in India region. This citrus fruit is largely cultivated in India, China, Vietnam, Indonesia, Southern Japan, Malaysia and Thailand. The Mosambi fruit is used as a source of juice and also eaten fresh, which is the important source of vitamin C and energy. In different countries it is called from different name (Table 2). Another important citrus fruit are *Citrus macroptera*, it is a semi-wild species which is cultivated in Malesia and Melanesia. This species is also cultivated in hill tracts of Bangladesh [8]. The commom name of this fruit is Melanesian papeda, wild orange, Cabuyao and Satkara [9, 10]. The fruit of *Citrus macroptera* has different phytochemical and pharmacological potentials such as cytotoxic activities, antimicrobial properties [11], antihypertensive, antipyretic activities, and appetite stimulant potentials [12, 13].

Orange fruit (*Citrus sinensis*) is extremely nutritious and rich in carbohydrates, different minerals, proteins and also in fat. It is shown that the peel of the Orange fruit contains approximately 10% its total weight. Lemon (*Citrus limon*) is also a significant medicinal plant belonging from the family Rutaceae. Research shows that the antibacterial property in lemon extracts effectively works against clinically significant bacterial strains [14]. All mentioned citrus fruits are common in sweet and sour flavor (Figure 1).

The Flowers and leaves of Citrus are generally strong scented, which contain numerous functional flavonoids and other compounds which are being used as insecticides, fungicides, and medicinal agents [15, 16, 17]. Research revealed that Extract of the peel, flowers and leaves of orange (*Citrus aurantium L*) are beneficial as pharmaceutical point of view to reduce the central nervous system related disorders.

Sweet orange is one of the members of Citrus genera; it is commenced from the region East Asia however it is consumed by all over the world country as a tremendous source of vitamin C. Citrus fruit are important source of natural antioxidant which improves the immune system. Flavanones and lots of polyethoxylated flavones are present in rich amount in the peel of citrus fruit as compare to other plants; these compounds are rarely available in other plants [18]. Citrus fruit contains many secondary metabolites such as Flavonoids, alkaloids, tannins, saponin etc. whereas secondary metabolites of citrus fruit that is isolated from primary metabolites are applicable in pharmaceuticals. They contribute to flavor, color and other characteristics of plant parts [19].

citrus fruit	citrus fruit
Citrus sinensis	*Citrus macroptera*
Citrus tangerine	*Citrus mitis*
Citrus junos	*Citrus australasica*
Citrus paradise	*Citrus mexima*
Citrus grandis	*Citrus unshi*
Citrus reticulata	*Citrus glaberrima*
Citrus aurantium	*Citrus climentina*
Citrus bergamia	*Citrus trifoliate*

Table 1 - Different species of citrus fruit

Country	Name of fruit
U.K	Narindz, Narineh
France	Orange, Sanguine
China	Tian, Cheng
Italy	Aranciodolce
Japan	Orengzi, Orenji
Spain	Naranjodulce
Germany	Apfelsine
India	Santra, Mosambi

Table 2 - International name of citrus fruit

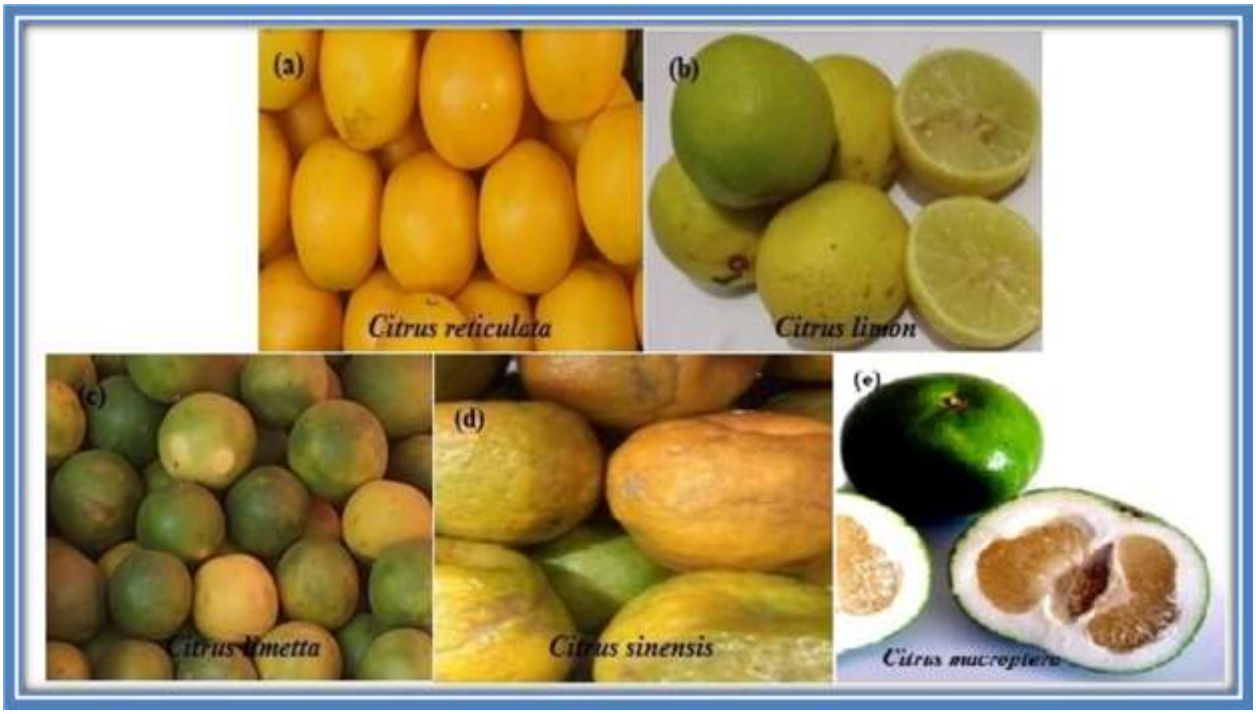

Figure 1. Different species of citrus fruits available in market

Citrus (Citrus L. from Rutaceae) is an important popular fruit crop in the world, that have active phytochemical substances which protect health. Beside this, it provides an abundant supply of numerous vitamins, specially vitamin C, folic acid, potassium and pectin. It is reported that the citrus fruit extracts and flavonoids present in citrus show a wide range of capable biological potency due to their phenolic profile and antioxidant properties [20, 21, 22].

In the season of winter a specific variety of citrus fruit is cultivated in north part of India. In Punjab and Rajasthan state a specific citrus fruit namely Kinnow or Tangerine (*Citrus reticulata*) is consumed for juice by different beverage industries and fruit vendors and it was shown that approximately 30–34% of kinnow peel is gained as a major derivative. So, this Kinnow peel is a wealthy source for health with useful compounds such as vitamin C, carotenoids and polyphenolic antioxidants [23]. Approximately 26% of citrus fruits are commercially used as juice production. The capability of citrus fruits and its derivative products on large scale production level is predictable at 15×106 tons and it constitute basically in seeds, peels and pulp residue [24, 25]. We all see that the Citrus fruits are particularly consumed all over the world as juice and usually its peel is discarded as waste material. The citrus fruit peel which is discarded is rich source of secondary metabolites having much antioxidant activity in compare to other parts of the fruit [26]. It is reported that the globally farming rate of citrus fruit has considerably enhanced in the last few years and it reached to 82 million tons by the years 2009–2010, in which mainly consumable citrus fruit variety i.e. oranges which commercially accounts for approximately 50 million tons [27], its 34% of production was used for juice, so approximately 44% peel yields as by-product [28]. So, a huge quantity of peel is produced every year. Citrus peel, which can also be called the primary waste, is a great source of molasses, limonene and pectin. It is used cattle feed in dried form [24]. Beside these, Citrus peel contains high quantity of sugar, protein and minerals. Citrus peel is a significant source of essential oils, they also contains lipids but in less amount.

Morphologically Citrus peel is made up of of flavedo (external part), it is mostly rich in vital oils and carotenoids, and the albedo (internal spongy part), is rich in pectin and phenols [29, 30, 31, 32]. Oil extracted from peel have strong aroma including refreshing outcome so it is mostly used as flavoring agent in food, beverage, cosmetic and pharmaceutical industries. Aromatic oils obtained from peel are safe and it has wide spectrum of biological activities in the form of antimicrobial, anti-inflammatory and antioxidants. It is also reported that Citrus fruit contains 90% terpenes, 5% oxygenated compounds and not more than 1% non-volatile compounds for example pigments and waxes [33]. An example of terpene is D-limonene, it has antimicrobial properties. Primarily, it shows the antibacterial activity against gram positive bacteria [34]. The internal spongy part (albedo), of Citrus fruit is rich in pectin and phenols.

2. PHYTOCHEMICAL PROPERTIES:

2.1 Phenolic compounds:

Most important bioactive compound for health benefits are phytochemicals, especially phenolic compounds present in fruits and vegetables. Phenolic compounds are also known as secondary metabolites which are synthesized

by different plants and it is available in the vacuoles of tissues. Different studies have shown that the phenolic compounds are present in both edible part and non edible part of the plants. The phenolic compounds are usually concerned in the plants protection against ultraviolet radiation or pathogenic violence [35].

The most important mechanisms for the antioxidant result of phenolic compounds in efficient foods having free radical scavenging activities. Several Reactive oxygen species (ROS), for example superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl) and the hydroxyl radical (HO) are the causative agents of pathogenesis in human beings [36, 37, 38]. The Phyto-phenolic compounds are effective source of preventing and treatment of free redical-mediated diseases for example diabetes [39], process of ageing [40], cancer [41], and cardiovascular disorder generated by scavenging of free radicals and quenching of ROS [42]. Lots of research has shown that the free radicals or reactive oxygen species available in the human organs creates oxidative degedradation to numerous bio molecules for example proteins, lipids and nucleic acids thereby leading to a number of degenerative disorders. The Phenolic compounds available in different fruits and vegetables peels have capacity to neutralize the free radicals and thus prevent the onset of degenerative diseases. Tetrazene and coumarins are several components available in lemon peel are able to scavenge free radicals by the electron or hydrogen-donating mechanisms, disrupting the chain reaction or removal of the ROS and RNS originator by quenching chain initiator catalyst [43]. During last decade from *C. sinensis* and kumquat (Fortunella japonica) some very effective phytochemical compounds named 4'-Geranyloxyferulic (GOFA) and boropinic acid are come in front for luxurious pharmacological drug for neuroprotective, cancer chemo defensive and anti-inflammatory activity [44]. The juice of *citrus lemon* fruit have rich amount of total phenolic and flavonoid. It was shown that the total phenolic content was 7.5± 0.56 mg/g and the flavonoids contents were 19.5 ± 1.15 mg/g [45].

Meat and meat products are mainly deteriorated due to lipid oxidation and auto-oxidation. The lipid oxidation has tendency to changes the color, texture, flavor, order and also the nutritional value of foods [46]. So, synthetic antioxidants are being used since long time to prevent the lipid oxidation. To overcome this demerit of use of synthetic anti-oxidants, it was replaced with powder extract of *Citrus reticulata* (kinnow) and the result revealed that the powder extract of kinnow are good source of phenolic compounds having free radical scavenging properties [47]. The bye-products i.e, peels and leaves of two citrus fruit (orange) varieties (*Citrus sinensis* L. and *Citrus aurantium* L.) are grown in Algeria, which is rich source of antioxidants [48].

The phenolic compounds have also capacity to act as phytoalexins [49] and supply to the sensory and organoleptic properties (color, taste, astringency) to important parts of plants such as vegetables and fruits [50]. So, a lots of studies have confirm that the presence of phenolic compounds, minerals, vitamins, essential oils, carotenoids and dietary fibers makes this citrus fruit a health promoting fruit.

3. PHARMACOLOGICAL PROPERTIES:

3.1 Flavonoids:

Flavonoids present in citrus fruit have very important biological as well as pharmaceutical activities; they have antibacterial, antidiabetic, antifungal, anticancer and antiviral activities [51, 52]. Flavonoids include a large family of compound synthesized in plants. It is low molecular weight compound. On the basis of structure flavonoids are polyphenolic compounds with a phenyl benzopyrene structure, it contains two benzene rings (C6) associated through three carbon-chains (C3), by a carbonyl group at C postion. Flavonoids are mostly present in plants as glycosides. Four types of flavonoids were found in citrus: flavanones, flavones, flavonols and anthocyanins [53]. The flavonoids of citrus fruit contains collection of glycosides, i.e, hesperidin and naringin and an additional group of O-methylatedaglycones of flavones for example nobiletin and tangeretin, these are two widespread polymethoxylated flavones (PMFs) [55]. It is reported that in citrus fruits peels there are greatest amounts of PMFs as compared to another parts of the fruits which is consumed [26, 55]. Flavonoids present in citrus have broad spectrum of health-related properties, such as antiviral, anti-inflammatory activity, anticancer, antimicrobial and antidiabetic activities.

From the biochemical study of flavonoids present in orange peel demonstrate that, it enhanced serum antioxidant capacity opposed to lipid peroxidation [56] and suppress the aged oxidative stress. This biochemical study also revealed that the flavonoids possess the advantageous effects as antitumor, anti-inflammation [57, 58] and antiatherosclerosis [59]. Now days, the dried form of tangerine peel (Citri reticulatae) is routinely used as Chinese medicine, pericarpium known as chen-pi for the treatment of several diseases such as dyspepsia, bronchial asthma and cardiac circulation, [60].

It has been reported that hesperidin which is the most predominant flavonoid in tangerine peel attain mild inhibitory activity against neuro inflammation however their combined effect is found to be significant [61].

3.2 Antimicrobial Activities:

Some phytochemical compounds, such as saponins, glycoside, tannins, terpenoids, flavanoids and alkaloids present in citrus fruit have been reported that it has antimicrobial activity [62]. It is also reported that terpenoids

present in citrus fruits are active against bacteria [63]. *Citrus macroptera* is greatly enriched with terpenoid compound and therefore may be most important source of antibacterial activity. In an experimental study of antimicrobial activity by disc diffusion technique, it was shown that the ethyl acetate extract of *Citrus macroptera* fruit extract showed wide range of antimicrobial activity against two gram positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis* and one gram negative bacteria, *Escherichia coli* out of six bacteria selected for experiment [11]. In another experimental work, it was shown that peel oil extract of *Citrus limetta* were constructive against different food borne pathogens including bacteria (*Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 6633, *Bacillus cereus* ATCC 14579, *Lactobacillus acidophilus* ATCC 4356 and *E. coli* ATCC 25922. In the result it was found that, peel oil showed maximum zone of inhibition against *B. cereus* ATCC 6633 (26 mm) followed by *S. aureus* ATCC25923 (21 mm) after 48 hours of incubation period at 37ºC, while the least zone of inhibition (11 mm) was resulted by *Fusarium oxysporum* ATCC 48122 at 48 hours of incubation at 25ºC [64]. Fruit peel extracts of some citrus verities such as *Citrus sinensis*, *Citrus aurantifolia*, and *Citrus limon* were investigated against the gastrointestinal pathogenic microbes. It was found that *Citrus aurantifolia and Citrus limon* showed maximum zone of inhibition against bacteria *Shigella* Spp., and *E. coli* strains, whereas *Citrus aurantifolia* was efficient against bacteria *Salmonella* spp. [65]. In a case study, the crude extracts (aqueous and ethanolic) of *Citrus limonum* fruits shows antibacterial activity against four pathogenic bacteria as, *Staphylococcus* sp, *Pseudomonas* sp, *Escherichia coli* and *Klebsiella* sp which was isolated from wound. Results showed that this fruit extract have antibacterial activity and its zone of inhibition are 20, 18, 20 and 15 mm (diameter) for ethanolic extract, and 15, 20, 11, and 10 mm for aqueous extract [66]. The antibacterial activity of *Citrus limon* was tested against *Acne vulgaris*. The juice of *Citrus limon* was applied in different concentrations as (20%, 40%, 60%, 80% and 100%) on the *Propioni bacterium acne*. Results showed that the *Citrus limon* juice has effective antibacterial activity at all selected concentrations [67]. Aqueous extract of *Citrus sinensis* fruit peel was studied against anti typhoid activity *in vitro*. Its result demonstrate that the aqueous extracts of *Citrus sinensis* fruit peel shows antityphoid activity against several bacteria such as *Salmonella typhi, Salmonella paratyphi* A and *Salmonella paratyphi* B [68].

It is reported that *Citrus aurantifolia* juice has potency to destroyed human immunodeficiency virus (HIV). From a laboratory experiment it was also shown that approximately 10% of *Citrus aurantifolia* juice formed 1000-fold decrease in HIV specimen [69]. In a recent research work, the aqueous extract of *C. limon* were tested antibacterial activity against four bacterial species viz. *S. flexneri, S. epidermidis, Citrobacter* species and *S. typhi*. The result showed that *S. flexneri* gives maximum zone of inhibition (15.2 ± 0.17 mm) In compare to *S. epidermidis* (13.4 ± 0.38 mm) at 1000 µg/disc concentration, while another two bacterial species viz. *Citrobacter* species *and S. typhi* showed zones of inhibition of 13.4 ± 0.32 mm and 9.7 ± 0.17 mm. at 700 µg/disc concentration [45].

3.3 Anthelmintic activity:

Anthelmintic activity of methanolic extract of *Citrus medica* was evaluated against Indian adult earth worm *Pheritima posthuma*. In this test various concentrations of extract were prepared and tested and the results were calculated in terms of time of death of the worm as well as time of paralysis. In this experimental work for standard Piperazine citrate (10 mg/ml) was used and as control, distilled water was used. The anthelmintic activity was possessed by the methanolic extract of *Citrus medica* [70]. Similarly, petroleum ether extract of the *Citrus sinensis* peels was studied for anthelmintic activity against Indian adult earthworms, *Pheretima posthuma,* it also illustrate dose dependent inhibition in the form of spontaneous paralysis, and genrated responses to pin-prick and the property were compatible with that of piperazine citrate [71]. The alcoholic extracts of *Citrus medica* peel showed anthelmintic activity *in vitro* against human Ascaris lumbricoides [72].

3.4 Anticancer activity:

Several epidemiological research and studies have exposed that the consumption of citrus fruits has tendency to decrease the risk of cancer. The eating/drinking of citrus fruit/juice has been reported that it is helpful for the decrease of certain types of human cancer [73]. It was shown that the biologically functionable compounds extracted from the *Citrus aurantifolia* seeds have the effectiveness to hamper human pancreatic cancer cells. On the other hand, the compounds purified from peel of *Citrus aurantifolia* had the potency to reduce the colon cancer cells [74].

3.5 Antioxidant activity:

The antioxidant activity of methanol and acetic acid extract of *Citrus macroptera* have been expansively studied different methods. In result it as shown that both methanol and acetic acid extract has potency of scavenging free radical and also prevent peroxidation process. It was also observed that methanolic extract showed much antioxidant potential compare to ethyl acetate extract in DPPH, NO, and lipid peroxidation assay. In another method, it has also shown that hot methanol extract of stem bark of *Citrus macroptera* have potential antioxidant activity (IC50: 178.96μg/ml) while cold methanol and dichloromethane extracts of the stem bark showed moderate activity with IC50 value of 242.78 μg/ml and 255.78 μg/ml, respectively [75].

In another experimental work, the antioxidant activity of *Citrus sinensis* peel extracted in different solvents was analyzed *in vitro* condition. Methonolic extract showed the maximum scavenging activity *in vitro* condition as compare to other solvent extracts i.e, ethanol, hexane, benzene, ethyl acetate, and chloroform having IC50 values were 65.44, 120, 138.45, 151.34, 170.34, and 185.35 with 55.6 % inhibitory concentration for ascorbic acid [76].

3.6 Anti-allergic activity:

Citrus fruits are also a rich source of anti-allergic compounds. Gencydo®, is a combination of citrus fruits such as aqueous quince (*Cydonia oblonga*) extract and *Citrus limon* juice are useful in alternative medicine for the treatment of patients suffering from allergic rhinitis or asthma. It was sheen that the Gencydo® has potency to decrease the degranulation and histamine release of IgE-activated basophilic cells as well as mast cells and repressed the IgE- and PMA/A23187-induced increases in IL-8, TNF-α and GM-CSF synthesis in mast cells [77]. The effects of the combined used of *Citrus medica* ssp. *limonum /Cydonia oblonga* (0.01 g/ml of both), individual food stuffs of *Citrus medica* ssp. *limonum* (0.01 g/ml) and *Cydonia oblonga* (0.01 g/ml) were tested on the immunological pathway which is involved in seasonal allergic rhinitis (SAR) [78].

4. CONVENTIONAL USES OF CITRUS FRUITS:

4.1 As digestive support: Due to its sweet aroma, citrus fruit (mosambi) juice facilitates the discharge of saliva from the salivary glands which helps in quick digestion. Beside this the flavonoids available in lime juice increase the digestive procedure by motivating the secretion of bile, digestive juices and acids. Hence, drinking mosambi juice frequently all over the day can ward off stomach problems, indigestion, nausea and faintness. The acids available in mosambi juice help in the exclusion of toxins from the bowel tracts, therefore relieve constipation. Sweet mosambi juice with a pinch of salt can provide immediate relief from constipation. Furthermore, it is efficient in case of stomach upsets, dysentery, diarrhea and loose motions as it is rich in potassium. Due to its tasty flavor, it protects from vomiting and nausea. It also helps in treatment of bloody dysentery.
4.2 Anti-diabetic benefits: Citrus fruit juice is beneficial for diabetic patients. To treat diabetes, it is recommended that, can mix 2 teaspoons of citrus (mosambi) juice, 4 teaspoons Amla juice and 1 teaspoon honey should mix and take this on an empty stomach every morning.
4.3 In the treatment of scurvy: This disease scurvy is caused by vitamin C deficiency characterized by swollen gums, frequent bouts of flu, clod and cracked lip corners. Due to rich in vitamin C, citrus fruit is effective in curing scurvy.
4.4 Immunity booster: Routinely consumption of citrus fruit juice regulates proper blood circulation by improving the function of the heart. This outcome is a great deal of healthier immune system.
4.5 Weight reduction: Being low in fat and calories, mosambi juice helps in reducing weight. You can drink a mixture of mosambi juice and honey to burn extra calories.
4.6 Beneficial in pregnancy: The citrus fruit juice provides a lot of calcium that are beneficial for both fetus and the mother to be.
4.7 Treatment of urinary disorders: Being rich in potassium, mosambi juice helps in treating urinary disorders such as cystitis. Cystitis is an inflammation of urinary bladder, also known as urinary tract infection (UTI). Mosambi juice boiled in water should be taken within a couple of hours after cooling for immediate relief in cystitis. Potassium facilitates the detoxification process of kidneys and bladder, preventing various types of urinary tract infections.
4.8 Remedy for Common Cold: Due to rich source of vitamin C, citrus juice helps in protection from common cold and enhances the body's resistance towards cold.
4.9 Anti-hyperlipidemic effects: Drinking mosambi juice reduces cholesterol and lowers blood pressure.
4.10 Remedy from various skin diseases: Due to rich source of vitamin C, it improves the skin colour naturally and is also used in several cosmetic products and substitute medicine supplements and vitamins. Citrus fruit is also helpful in treatment of Pigmentation, Spots and Blemishes of skin.
4.11 Reduction of Swelling and Pain: Applying a mixture of citrus fruit (mosambi) juice and castor oil on the affected area can lessen swelling and pain**.**

5. CONCLUSION:

Currently there is much interest worldwide for herbal medicines having pharmacological properties of the bioactive compounds to treat various diseases. A lots of drugs obtained from herbs have entered in international market through traditional medicines. Citrus fruit is one of the sources of herb which is known for its medicinal as well as nutritional properties. This citrus species is rich source of vitamin C. All parts of this citrus species plant such as fruit juice, peel and flower are used as traditional medicine. Due to the low cast and easily availability of this citrus fruit residue, this is also discarded as waste material in the environment have potential source of nutraceutics. So it can

be told that, this citrus plant is unique source of bioactive compounds having varied medicinal as well as nutraceutical properties. Several pharmacological properties of this citrus fruit are reported as antimicrobial activity, antioxidant activity, anti-allergic activity, anticancer activity, antidiabetic activity etc. The extract from fruit peel has important application in food and pharmaceutical industries as a rich source of bioactive compound. This review paper communicates the pharmacological as well as therapeutic property of *Citrus* fruits as talented nutraceutical due to its safety and efficiency. The recent information related to this medicinal plant serve as the baseline data which impose to do broad study for the development of novel bioactive compounds and exploration for its biological activities. Therefore, more research is needed to fix bioavailability and benefits of these citrus fruit.

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