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Potential Phytoconstituents of Some Fruit and Vegetable Peels Against Oxidative Damage, Inflammatory and Cytotoxic Diseases

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Abstract

Food products industry generates many undesired waste materials. Proper use of these by-products may minimize problems with waste disposal and act as a possible new source of fats and proteins for food and feed use. Peels, and seeds resulted from fruit and vegetable manufacturing are effectively utilized as a promising source of many phytochemicals and antioxidant agents. The produced by-products are an important and vital source of many carbohydrates, minerals, organic acids, dietary fibers and phenolic compounds that have a broad spectrum of antiviral, anticancer, antimicrobial, and cardioprotective action. Hence, there is poor available information about the beneficial values and use of theses by-products, this review article is concerned about the variety of the biological activities could be exerted by these remarkable secondary metabolite rich sources.

Key words: Phytoconstituents, Peels, Oxidative Damage, Inflammatory, Cytotoxic**.**

1. Introduction

Food products industry generates many undesired waste materials. Owing to utilization of various fruits and vegetables, numerous methods and variety of products, the produced wastes are highly variable **[1].**

Food processing industries, vegetable markets and restaurants manufacturing many decomposable wastes in immense amounts, yielding between 25 percent and 30 percent of non-edible products **[2].** Management of such organic waste is a big problem worldwide. Greenhouse gases such as methane and nitrous oxides were produced either in the landfill or by composting by the disposal of these decomposable wastes. The decomposable waste that is dumped into the environment can be used to produce value added bio-product which in turn decreases greenhouse gas produced from it **[3].**Proper use of these by-products may minimize problems with waste disposal and act as a possible new source of fats and proteins for food and feed use **[4].**

Fruit waste recycling is one of the most novel trend to produce new products that meet the critical requirements for human being nutrition. The combined efforts for reusing waste materials after the manufacturing process and recovery of valuable products greatly decreases the amount of wastes, as well as increases the environmental profile **[5]**.

Depending on different plant species, various active constituents such as antioxidants, like vitamins E and C, phenolics, flavonoids, and carotenoids e.g. lycopene may exist. The by-products; peels, and seeds resulted from fruit and vegetable manufacturing are effectively utilized as a promising source of many phytochemicals and antioxidant agents. The fruits and vegetables are plentiful in many bioactive constituents, as many flavonoids, essential fatty acids, and alkaloids. Additionally, the produced by-products can exhibit similar or greater amount of antioxidants and anti-inflammatory constituents than the original ones can do **[6].**

New features relating to using these waste products as by-products for further exploitation in the manufacture of many food additives with high nutritional values have gained growing interest as they are high-value substances and can be economically attractive for recovering. The produced by-products are an important and vital source of many carbohydrates, minerals, organic acids, dietary fibers and phenolic compounds that have a broad spectrum of antiviral, anticancer, antimicrobial, and cardioprotective action. As a result of increasing risk

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of many diseases, a critical need of the hour is to search for new promising natural products with unique mode of action. The natural by-products afford extremely great opportunity for finding new significant treatments. The peels produced from the fruit and vegetable are dumped into the environment as agricultural wastes might be used as an antimicrobial agent. However, due to poor available information about their beneficial values, the use of theses by-products is minimal **[4].**

The amount of total losses for these commodities is calculated to be approximately 20-30% of total production, 10.91 % of pulp and seed (core) by-products were produced by sliced apples, 16.05 % of peels were produced by peeled mandarins, 6.51 % of seeds and 8.47 % of peels were formed by diced papayas, 9.12 % of heart, 13.48 % of peels, were formed by pineapples. Also, mangoes give 13.5% of seeds, and 11% of peels. Great consideration should be done to use these by-products in order to develop promising and effective alternatives for medical application. In 2003, FAO stated that 16.8 million tons (MT) of vegetables and fruits processing producing 3.36 MT of the by-products. The failure in reusing these by-products may produce excessive undesirable wastes and deplete the natural resources **[6]**.

2. Phytochemical Composition of the Fruit and Vegetable Peels

Various studies conducted on fruit and vegetable peels revealed the existence of many effective components, that could be utilized in several pharmacological or pharmaceutical applications. Recently, researchers extracted large number of active ingredients from different vegetable and fruit peels and test them as antibacterial, free radical scavenger, anticancer and anti-inflammatory agents **[7, 11, 12].** Plants produce a wide range of secondary metabolites named as phytochemicals, these compounds are responsible for plant defense against numerous pathogens, and in the last few decades many classes of phytochemicals have proved to reduce the risk of several diseases such as tumors and cardiovascular disease. Currently, there is a developing awareness in discovering effective and significant active constituents to be a safe alternative to the artificial materials that are usually consumed in the nutritional, therapeutic and cosmetic applications**.** Apart from dietary fiber, the human health benefits are primarily due to presence of various micro and macro constituents in the fruit and vegetable peels such as chlorophylls, carotenoids, flavonoids, minerals, and vitamins, etc., it is reported that dietary intake of flavonoids almost certainly minimize the risk of several diseases associated with oxidative stress, together with cancer diseases **[8].**

The products and by-products produced during the minimal processing of the vegetables and fruits were examined for the phytochemical constituents and free radical scavenger activity. It was noticed that the total contents of phenolic and flavonoidal compounds were higher in the by-products than that found in the final products, being more obvious in the seeds and peels of mango. These components might probably be essential for antioxidant activity. Numerous researches have proved that the values of active constituents in mango′s peels and seeds are higher than that of the edible tissue **[6]**.

Gorinstein *et al*., (2001) [9] stated that the amount of total phenolic compounds in the peels of citrus family were about 15% greater than that of the fruit tissues. Also, Skins from peeled apples, and peaches have double the amount of total phenolics existed fruit. While the edible pulp of bananas (*Musa paradisiaca*) contains 232 mg/100 g of dry weight phenolic constituents, this quantity is about 25% of that exists in the peels **[10].**In the same way, another study reported that the peels of pomegranate contain 249.4 mg/g of phenolic components as compared to only 24.4 mg/g phenolics examined in the fruit pulp. Also, the peels of apple contain many phenolic compounds with a dry weight of up to 3300 mg/100g **[11].**

Moreover, grape seeds and skins contain huge number of phenolic constituents, primarily mono, oligo, and polymeric proanthocyanidins. The peels and seeds of tomatoes are wealthier source of phenolic compounds than that in the pulp. Another study examined the quantity of the phenolic compounds in twelve genotypes of tomatoes, and, generally, the less values were detected in the flesh, amounting 9-27mg/100 g, while10 - 40 mg/100 g in the peels **[12].** Additional research informed that the total phenolic compounds in the peels, seeds, and pulp of tomatoes were 29.1, 22.0, and 12.7 mg/100 g, respectively. So that, it was concluded that tomato′s peel has significantly greater values of active constituents than that reported in the pulp and seeds **[13].**Generally, the phenolic content of the by-products is up to 10 times greater than that of pulp.

2.1. Phenolic Compounds

The term “phenolic” or “polyphenol” is chemically defined as substances that contain a benzene ring with one or more hydroxyl groups **[14]**.Metabolic flows of the polyphenols in plants are illustrated in **Figure 1**.Phenolic compounds are well known as one of the most abundant classes of the phytochemicals having significant health potentials. Detailed classification of the polyphenols is shown in **Figure 2**.

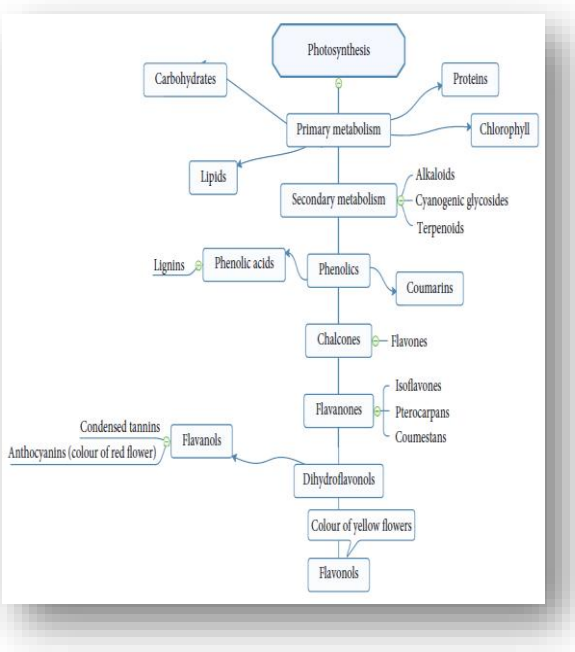

Figure 1. Metabolic flows of the polyphenols in plants.

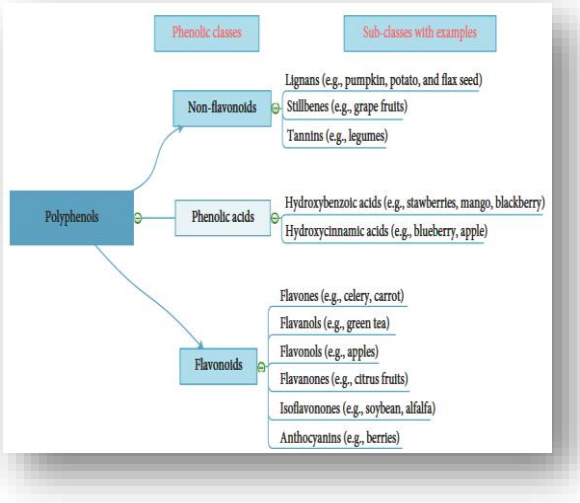

Figure 2. Detailed classification of the polyphenols.

Phenolic Compounds as Antioxidants

Phenolics are a diversified group of secondary metabolites of plants, which comprise of simple phenolic, phenolic acids (derivatives of benzoic and cinnamic acid), lignans, coumarins, flavonoids, stilbenes, flavonolignans and tannins. Many of phenolic compounds have displayed significant antioxidant activities as oxygen scavengers, peroxide decomposers, metal chelating agents, and free radical inhibitors. Besides antioxidant effect, phenolic compounds have a wide range of activities including antitumor, antiviral, antibacterial, cardioprotective, and antimutagenic effects **[15]**.

Peels from the apple show high values of the phenolic compounds and so it could treat several diseases. The total free radical scavenging activity of the peels was 2.5 times greater than that presented in the pulp **[16].** The traditional processing of apple juice resulted in phenolic-poor juice and only 3-10% of the fruit's antioxidant activity was produced from the fruit.

The antioxidant properties of apple pomace polyphenols were evaluated using different model systems; DPPH test, and superoxide ion radical scavenging effect. The examined polyphenols were epicatechin, its dimer (procyanidinB2), flavonoid aglycones and glycosides, and several phenolic acids. All the compounds exhibited strong free radical scavenging effect by, 2-3 times and super oxide anion radical-scavenging effect by 10-30 times greater than the antioxidant effect of vitamins C and E **[17].**

2.2. Flavonoids

Flavonoids are compounds with low molecular weight which are responsible for the bright color of fruit and vegetable peels, pulp, and leaves. More than 9000 flavonoids have been recognized to date. Flavonoids feature a basicC6–C3–C6, 15-carbon skeleton (**Figure 3**). They consist of 2 benzene rings (A and B)attached by a pyran ring. Flavonoids are divided according to the existence of an oxy moiety at C4, the double bond C2 = C3, or presence of OH group at C3 of the heterocyclic ring **[16].**

The biological effects of flavonoids increase with the degree of hydroxylation of the B ring**.** The basic structure of flavonoids allows various substitution patterns in the benzene rings A and B within each class of flavonoids **[18].** The abundance of flavonoids exists from various combinations of OH and OCH_3 group substitutions. Moreover, flavonoids can also be categorized by variants in the ring C ring to flavones, flavanones, flavonols, isoflavones, flavans, and anthocyanidins as illustrated in **Figure 3 [19].**

Flavonoids as Antioxidants

The antioxidant effect of flavonoids is depending on presence of *ortho* dihydroxy substitution in ring B, the presence of double bond at C2 and C3 in addition to existence of 4-oxo moiety in ring C**.** Flavonoids with OH group at C3 of the C ring are named flavonols, while the flavonoid with saturated bond at C2-C3 and without hydroxyl group are termed flavanones and flavones**[16].**

It was well known that peels of *Citrus* fruits enriched in various polymethoxylated flavonoids which are uncommon in other plant peels. Regular consumption of food rich in flavonoids could protect the elderlies from many cardiovascular diseases. **Figures(4& 5)**illustrate the basic structural formula of the flavonoids detected in citrus peels such as hesperidin, neohesperidin and naringin as well as tangeretin, sinensetin, and nobiletin**[20].** The biological activities of flavonoids are linked to their antioxidant actions**,** that protect the brain from different degenerative diseases such as Alzheimer **[21].**

In 2020, new *in vitro* study proved that the flavonoids in citrus peels have prevented oxidation of LDL and have decreased the thrombotic tendency, but their effects on atherosclerotic problems not identified yet **[22].**

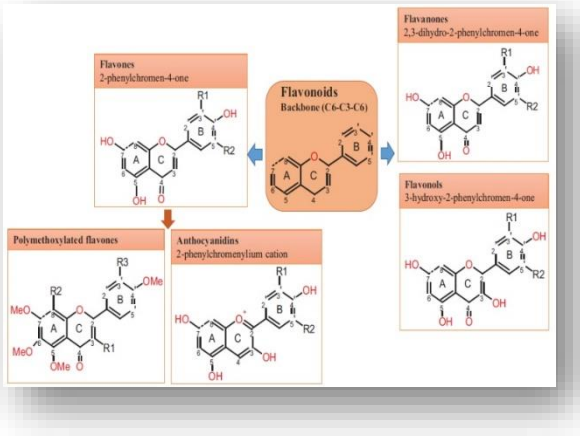

Figure3.Main skeleton of flavonoids and their classes.

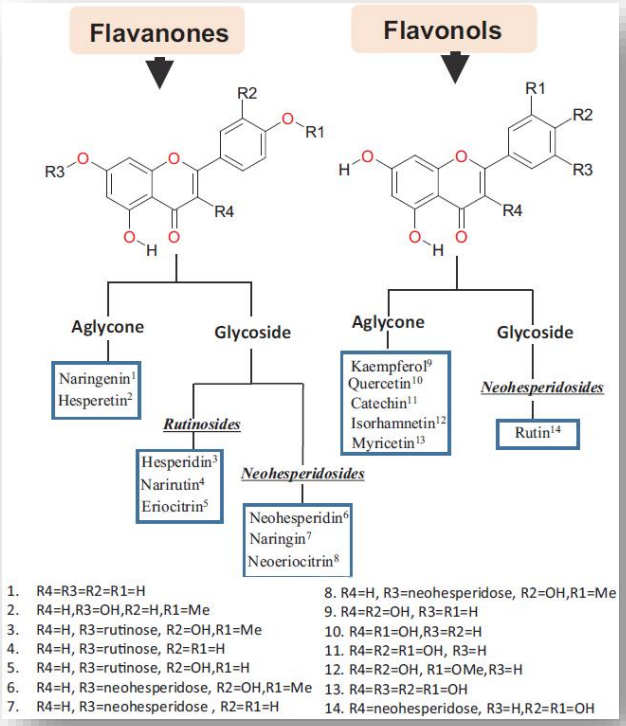

Figure 4.The structural formulas of flavanones and flavonols in citrus peels and their subclasses.

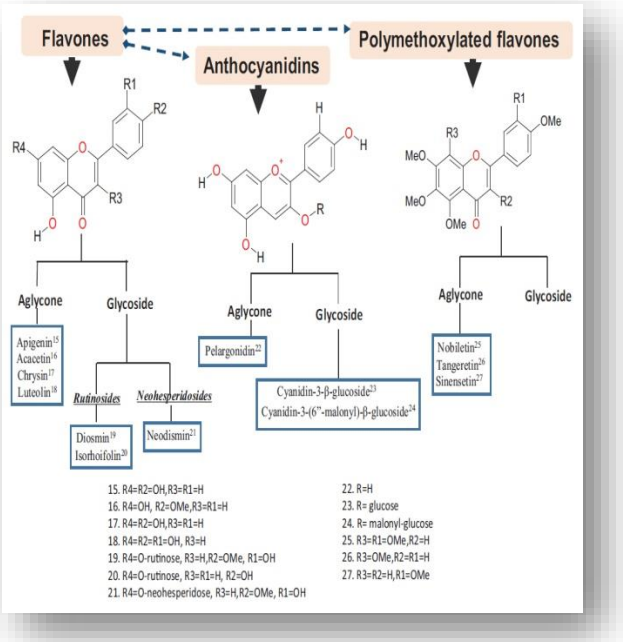

Figure 5.The structural formulas of flavones, anthocyanidins, polymethoxylated flavones in citrus peels and their subclasses.

2.3. Tannins

Catechin, epicatechin, epicatechingallate and epigallocatechin were the main constitutive compounds (monomer units of tannins) in the grape skin tannins. All the investigated compounds proved strong antiradical effect. Catechin and epicatechin exhibited significant free radical scavenging capacity. Recent studies reported a wide range of biological activities such as hypoglycemic effects, radioprotective capacity, the inhibition of antioxidant enzyme expression, protecting from the oxidative injury in mice brains, in addition to anti-inflammatory properties **[23].**

The high efficacy of grape seeds as potent anti-oxidative agent has been verified by the fact that they act as natural potent anti-oxidative through inhibiting the lipid peroxidation beside to the protection role against the oxidative damages **[24].**

Tannins as Antioxidants

Recent research has verified the anti-oxidative properties of the grape skin extract both *in vivo* and *in vitro* studies. Grape seeds produce greater anti-oxidative effect than the skins and the flesh parts**.** The antioxidant activity are tested mainly through scavenging action on DPPH, in addition to chelation of the metals, beside to reducing of hydroperoxide development and their action on cell signaling pathway and the gene expressions**[23].**

2.4. Limonoids

Limonoids are a huge family of polycyclic compounds extracted mainly from peels of citrus fruits**,** such as lemons, oranges (both sweet and sour), and grapefruits. Limonoids are considered as highly oxygenated triterpenoids containing comparatively large number of oxygens in their basic skeleton. They exist as both free aglycones and corresponding β-D-glucosides. Citrus seeds and peels contain75% and 85% aglycones, while the predominance of the glucosides in juices and pulps were 60% and 75% respectively **[25].**

Limonoids as Antioxidants

Now days, limonoids are studied for a wide-ranging activities such as free radical scavenging, antiviral, antimicrobial, and anticancer effects. Lemon seed (*Citrus limon*) extracts containing a high percentage of limonoid glucosides have been studied for their antioxidative capacity and antineoplastic effects against human breast adenocarcinoma (MCF-7) cells**[25]**.

2.5.**Anthocyanin**

Anthocyanins are coloring water soluble pigmentation compounds classified into the flavonoids class. The pigments are founds in form of glycosylion.The color and taste of many fruits and vegetables was due to anthocyanin pigments. Anthocyanins act as red color in acidic conditions, while blue colored anthocyanins occur in alkaline PH **[26].** The basic structure of anthocyanin is shown in **Figure 6**. Increasing the interest due to their strong antioxidant activity and their potential application for human health. Many evidences of the preventive and therapeutic function of anthocyanin in various types of chronic diseases. Moreover, several studies have focused on the impact of anthocyanins in cancer prevention **[27]**.

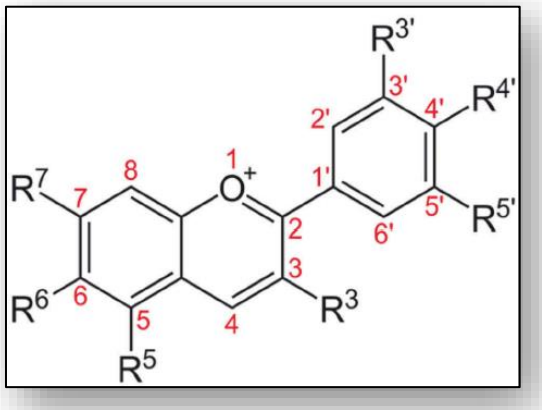

Figure 6.**Basic structure of anthocyanin.**

Anthocyanin as Antioxidants

Several scientific studies have long-established the effect of the regular intake of the colored vegetables and fruits as powerful antioxidative agents. Additionally, black carrot, and red cabbage - the main source of anthocyanin- are well thought out as an important food for prevention of many chronic diseases **[28].** In folk medicine throughout the world, the functions of anthocyanin pigments as therapeutic agents have been well known. For example, anthocyanins presented in *Hibiscus sp.* have traditionally been used for treatments of liver diseases, and as hypotensive agent. Another example, bilberry′s anthocyanins have traditional applications against several microbial attack, and many gastrointestinal complications **[29].**

Apples are rich in anthocyanin contents which exist in the peels, more than that in the flesh part. The nutritious studies recommended the regular dietary intake of the whole apples without peeling as it is rich in numerous antioxidant compounds which benefits the human nutritional health**[30].**

The free radical scavenging effect of anthocyanins depends on their chemical structure; number and position of the OH groups and the degree of unsaturation. Where, anthocyanins have a potential free radical scavenging activity double that of vitamin E **[26].**

3. Fruit and Vegetable Peels as Natural Antioxidants

Antioxidants are necessary and important for sustenance of living beings. They protect cells from the damage caused by unstable molecules known as free radicals. Oxidation reactions can create free radicals, which injury the cells**.** Antioxidant agents terminate the oxidation chain by get rid of the free radicals or by being oxidized themselves **[31].**

The mechanism of action of the antioxidants can be illustrated either by donating electrons to free radicals existing in the system and interrupt the oxidation process or by eliminating the ROS and RNS**.** In addition to defending cells against damages accompanied with many human disorders, antioxidant agents perform an important action in preventing harmful changes in the taste and nutritious value of food**[32].**

A new interest in the antioxidant studies is focusing in finding a potential natural alternatives for the synthetic antioxidant drugs. A huge range of phenolic compounds proved significant free radical scavenging effect has been recommended. At this time, several researchers examined the potential effects of the phenolic compounds on the cardiovascular system by inhibiting the oxidation of LDL and so that, reducing the evidence of atherosclerosis **[33].** Many phenolic compounds are existing as glycosides or might present as esters**[31].** As a result of the wide-ranging of the phenolic compounds, they could be categorized to several classes of which phenolic acids, flavonoids and tannins are observed as the major phenolic constituents**[32].**

Structure of the phenolics is a determining factor of their antioxidant activity and metal chelating effect; this is discussed in the structure activity relationships (SAR). The great antioxidant effect of the phenolic compounds might be attribute to the presence of OH groups. Also, the activity depend on their absorption and metabolism, that are affected by their structure **[31].**

The phytochemicals extracted from fruit and vegetable peels are able to neutralize the free radicals and so that they can play a key role in treatment of many health disorders**.** Their activities of are expressed in terms of the powerful reducing effects potential free-radical scavenger **[14].**

- **Banana peels (*Musa acuminata*) as natural antioxidant:** The antioxidant potential of crude extracts from green and yellow banana peels were examined and the results pointed that green banana produced more significant effect than that of yellow ones **[34].**

  The impact of stage of fruit maturity and the used parts either peels or fleshy on presence of the antioxidative components in banana was investigated by **[35]**. Values of total phenolic content (TPC) and total flavonoid content (TFC) in banana peels were higher than those presented in banana pulp. Also, green banana exhibited higher values of TPC and TFC than those found in the ripe fruit.

- **Potato peels as natural antioxidant:** *Solanum tuberosum* L. peels produced from potato processing, can be used as a novel promising tool of dietary fiber, and phenolic compounds. More than 50% of the active constituents are located in the peels and adjacent tissues and decrease gradually towards the center of the tuber as illustrated by **Friedmen (1997)[36].** Ferulic acid was recognized as the major antioxidant compound present in potato peels **[37].**

- **Watermelon peels as natural antioxidant:** The therapeutic potential of watermelon (*Citrullus lanatus*) has been reported and has been attributed to existence of various antioxidant constituents **[38].** From them, citrullin and lycopene in addition to 4–hydroxybenzoic acid **[31]** have been proved to show a prominent role in the treatment and management of several disorders such as tumors and cardiac diseases **[39].**

- **Cucumber peels as natural antioxidant:** *Cucumis sativus* L. peels is well known as a low-priced source of flavonoids and could be utilized as an important source of antioxidation in many industrial applications **[40].**

  In 2008, **Zeyeda *et al*. [41]** calculated the amount of phenolic constituents in some vegetable peels and

reported them in descending order as tomato peels, cucumber peels, watermelon peels, and potato peels. The main phenolic compounds in cucumber peels were recognized as chlorophylls, pheophytins, phellandrenes and caryophyllenes in the range of 1.5 – 3.5 mg/g. among them, cholrophylls and pheophytins were well-known with the greatest contents in peels of cucumber and watermelon.

In short, vegetable and fruit peels are a great and cheap source of various bioactive compounds especially antioxidants. Highly efficient methods of extraction of these compounds are available which made them available for uses in food industry and in therapeutic application. Compared to the synthetics having possible carcinogenic effects it is safe and ecofriendly.

4. Fruit and Vegetable Peels as Anticancer Agents

Cancer is the life threatening disease described by the abnormal proliferation of cells which attack the adjacent cells causing the damage of those tissues. It is considered as one of the most principal causes of human death worldwide **[42].** The occurrence of the disease is increasing more quickly in Africa and Asia, to about 70% of the mortality in the world**.** Various reports have been focusing on the development of agent for cancer remedies**.** Unfortunately, the chemotherapy have many adverse drawbacks on normal functions, for example inhibiting the functions in bone marrow, causing nausea and vomiting, in addition to hair fall **[43]**.

Contrariwise, natural antioxidant agents and several phytochemicals have been acted as cytotoxic adjuvant agents in cancer treatment protocols as these natural compounds have a potential anti-proliferative activity**.** Therefore, the continuous studying to develop new cytotoxic substances from natural source become a critical issue for finding the potential safe and effective drug with less adverse side effects since the fruit and vegetable peels have several benefits **[44].**

Over many decades, around 200 new chemical compounds have been approved for the battle against cancer, more than 50% of the marc originated from natural source and their modification have many benefits **[45]**. Due to their varied structures, these new compounds perform a key action in selective inhibiting the tumor proliferation **[46].**

- **Citrus peels as anticancer agents**

Dietary flavonoids interfere with the activation of carcinogens, promote the detoxification of carcinogens, scavenge free radical species, regulate the progression of the cell cycles, and prevent cell proliferations, beside to inhibition of the hormones or growth-factor activities **[47].**

Polymethoxylated flavones as nobiletin, tangeretin, and sinensetin existed in citrus peels were able to inhibit the proliferation of several malignant cells because of their inhibition activity on the endothelial cell proliferation through reducing the vascular endothelial growth factor activity **[48],** in addition to potent scavenging effects on the ROS, regulation of the cell cycles, avoiding begin of the cancer evidence, enhancement of the apoptosis, minimizing the oncogene effects, inhibiting of the angiogenesis, along with modulation for activities of many hormones and growth factors **[49]**.

- **Onion peels (*Allium cepa*) as anticancer agents**

Quercetin exists in the peels of onion, grapes, and apples, is widely studied natural compound due to its significant effects on the cell proliferations. It displays inhibitory growth action against a number of tumor cells such as human liver (HepG2), immortal human HeLa cells, human epidermoid carcinoma (A431), colon (COLO 320 DM), human pancreatic (PaCa2), human ovarian (Caov-3), and human breast (MCF7) cancer cells **[50]**. Actually, the strong antiproliferative activity of quercetin is might be attributed to inhibition of the proteinkinase C (PKC) pathway **[51]**.

The antioxidant and cytotoxic effects of the flavonoids are associated to their definite structural skeleton, as they may contain substituents in both the A and B rings of the flavonoid structure. Studies of melanoma cell lines using many citrus peel flavonoids illustrated that existence unsaturation at C2 and C3 in the ring C, in conjugation with 4-oxo group, is a key factor in this biological activity. The presence of more than 3 OH or OCH_3 substitutions in ring A and B is suggestively improve the antiproliferative action against several human cancer cell lines**[52].**

- **Pomegranate peels as anticancer agents**

Ellagitannins, proanthocyanidins, ellagic and gallic acids, unicalagin and punicalin are found in peels of pomegranate (*Punica granatum*), have been shown that

besides acting as antioxidant agents, pro-oxidant effects are reported, especially at high concentrations **[53].**The antiproliferative effect of punicalagin, ellagic acid, and total pomegranate tannin extract against several human oral, colon and prostate tumor cells was studied**.** According to the results of this research, all pomegranate ingredients reduced the cell viabilities in the dose dependent mode in most of the tested cancer cell lines **[54].**

- **Eggplant peels as anticancer agent**

Glyco alkaloid is classified as one of the steroidal glycoside classes of which are they are basically varied and exhibited wide ranging spectrum of therapeutic effects like antimicrobial, anti-oxidant, and cytotoxic effects **[55]**. It was greatly noticed that existence of sugar substitutions are critical for their therapeutic effects **[56]**. Solasodine aglycone exhibited anticancer effect against human liver and colon cancer cells **[57]**.In 2019, three steroidal glycosides (**Figure 7**)in the methanolic extract of eggplant (*Solanum melongena*) peels were *in vitro* tested against 5 human cancer cell lines; liver (HepG2), breast (MCF7), colon (HCT116), larynx (HEP2), and cervix (HeLa)**.**These compounds proved potent cytotoxic effects against the tested cancer cell lines specially the liver cancer cell line which was significantly inhibited **[58].**

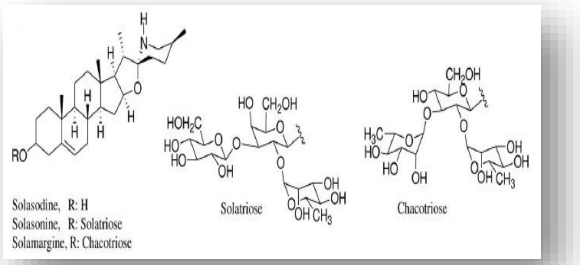

Figure 7.Structures of the isolated compounds from *Solanum melongena* peels.

. Fruit and Vegetable Peels as Anti-inflammatory Agents

Inflammation is considered as a normal reaction of the living tissue against injuries. It considered as a body defensing response to remove or reduce spreading of the damaging substances typically characterized by increasing in tissue permeability and endothelial leukocyte influx of blood into the interstitium, resulting information of edema**.** Inflammation and pain are common non-specific indexes of various diseases. Many inflammatory mediators such as histamine and prostaglandins are existed abundantly in the inflammation sites **[59].**Prostaglandins are universal mediator that direct and control cell responding against various pains and inflammations**.** The therapeutic action of many anti-inflammatory drugs was produced through blocking the synthesis or hindering the effects of the inflammatory mediators **[60].**

The most extensively used treatments are involving inhibition of cyclooxygenase (COX) by NSAIDs and opioids which are effective for treating the inflammation and pain**.** These drugs block COX-1 and COX-2 enzymes involved in production of prostaglandin. However, their chronic using mainly in patients with arthritis or other chronic inflammatory diseases is accompanying with many adverse effects such as ulceration, gastrointestinal perforation, bleeding and renal toxicity mainly due to the blockade of COX-1. Therefore critical needs arise to develop new promising natural anti-inflammatory products having great effects and with less drawbacks to be acting as safe replacement for the chemical therapeutic drugs **[61].**

- ***Citrus* fruit peels as anti-inflammatory agent**

Many studies have reported that peels of *Citrus* family have various therapeutic activities like antioxidant, anti-cancer, antipyretic, hypolipidemic, and many more**.** Recent literatures also examined the anti-inflammatory and analgesic activities for several *citrus* fruit peels **[60].**

The anti-inflammatory activity of *Citrus* fruit peels is more significant at the later phases of the inflammation. Therefore, it can be concluded that the inhibitory action on carrageenan-induced inflammation might be due to inhibiting cyclooxygenase enzyme and thus hinder prostaglandin synthesis **[62].**

Many phenolic compounds in *Citrus* fruit peels are exhibited to have powerful anti-inflammatory effect which was reported by **Roy *et al.* (2010) [63]**. Furthermore, the flavonoids are recognized for inhibition of the enzyme prostaglandin synthetase, more specifically the endoperoxidase and reported to exhibit potent

anti-inflammatory activity**[60].** In addition to many essential oils exhibited strong inhibitory action against the cytokines production, limonoid existed in the citrus peels have potential cytotoxic and anti-inflammatory effects **[64].**

Also many studies focused on the effect of tannins in the anti-proliferative effect **[65].**Apart from this, phytosterols have been stated to inhibit some of the pro-inflammatory cytokines including C-reactive protein **[66]**and alkaloids have been proved to have pain-killing effect suggesting their role against inflammation **[67]**.

The anti-inflammatory action of triterpenoids have been related to several mode of actions through inhibition of lipoxygenase and cycloxygenase activities **[68].**Hence the analgesic and anti-inflammatory activity produced by the citrus peel extracts may be attributed individually or collectively to presence of flavonoids, limonoids, alkaloids, terpenes, steroids, and tannins **[60].**

- **Mango fruit peels as anti-inflammatory agent**

Mango (*Mangifera indica*) is an important seasonal, tropical fruit with brilliant colorful and health promotion effects**.** The peels of mango fruit have several secondary metabolites such as polyphenols, flavonoids, steroids, terpenoids and saponins which corroborates with the reports of **Rakholiya *et al*., (2016) [69].**Mango peels possess more values of total phenolic content and total flavonoids content than that of the flesh**.** Many researchers stated that the mango peels have various bioactivities such as antioxidant, anti-proliferating **[70]** and anti-inflammatory activities **[71].** The change of green to yellow color was examined in mango peels as a result of reduction of hydrogen or electron donor **[72].**

According to **Knodler *et al*., (2008) [73],** mango peels have many polyphenolic compounds which might be responsible for the anti-inflammatory activity.

- **Pomegranate fruit peels as anti-inflammatory agent**

Punica granatum L. is consumed universally as fresh fruit and by juice. It is recognized for its free radical scavenging, antibacterial, anti-inflammatory and anti-proliferative activities **[74].** The peels mainly have hydrolysable tannin named punicalagins(88.8%) that is ester of gallic acid **[75],** this compound is extensively known for the antioxidant and anti-inflammatory activities **[76]** through suppression expressing of IL6 and CXCL8 and hindering the nuclear factor kappa B (NF-Kβ) pathway **[77].**

Conflicts of interest

There are no conflicts to declare.

References

[1] William P.T., Water treatment and disposal. John Wally (eds.) *Greet Britain* pp. 2005: 9.

[2] Ajila C.M., Aalami M., Leelavathi K., Rao UJSP., Mango peel powder: a potential source of antioxidant and dietary fiber in macaroni preparations. *Innov Food SciEmerg.*,**11**, 219–224 (2010).

[3] Saramanda G. , Kaparapu J., Antimicrobial Activity of Fermented Citrus Fruit Peel Extract. *Int. Journal of Engineering Research and Application*, **7** (11), 25-28 (2017).

[4] Kamel B.S., Kakuda Y., Fatty acids in fruits and fruits products. In: Chow CK, (Ed) *Fatty Acids in Food and their Health Implications* (2nd Edn), Marcel Dekker, New York, 239-270(2002) .

[5] Kumar K. A., Narayani M., Subanthini A. , Jayakumar M., International *Journal of Engineering Science and Technology*, **3** (6), 5414-5421(2011).

[6] Ayala-Zavala J.F., Rosas-Dominquez C., Vega-Vega V., Gonzalez-Aguilar G.A., Antioxidant enrichment and antimicrobial protection of fresh-cut fruits using their own by-products: looking for

integral exploitation. *J Food Sci.* **75**, R175–R181(2010).
[7] Saleem M., Saeed M. T., Potential application of waste fruit peels (orange, yellow lemon and banana) as wide range natural antimicrobial agent. *Journal of King Saud University – Science*, **32** , 805–810(2020).
[8] Janabi A. H. W., Kamboh A. A., Saeed M., Xiaoyu L., BiBi J., Majeed F., Naveed M., Mughal M. J., Korejo N. A., Kamboh R., Alagawany M., H. L., Flavonoid-rich foods (FRF): A promising nutraceutical approach against lifespan-shortening diseases. *Iran J Basic Med Sci*., **23**(2), 140–153(2020).
[9] Gorinstein, Martin-Belloso O., Park Y.S., Haruenkit R., Lojek A., Ciz M., Caspi A., Libman I. , Trakhtenberg S., Comparison of some biochemical characteristics of different citrus fruits. *Food Chem.*,**74**,309-315(2001).
[10] Someya S., Yoshiki Y., Okubo K., Antioxidant compounds from bananas (*Musa cavendish*). *Food Chem.*, **79**, 351–354(2002).
[11] Wolfe K.L., Liu R.H., Apple peels as a value-added food ingredient. *J Agric Food Chem.*,**51**,1676–1683(2003).
[12] George B., Kaur C., Khurdiya D.S., Kapoor H.C., Antioxidants in tomato (*Lycopersium esculentum*) as a function of genotype.*Food Chem.*, **84**,45–51(2004).
[13] Toor R.K., Savage G.P., Antioxidant activity in different fractions of tomatoes. *Food Res Int.*, **38**, 487–494(2005).
[14] Swallah M. S., Sun H., Affoh R., Fu H., Yu H., Antioxidant potential overviews of secondary metabolites (polyphenols) in fruits. *International Journal of Food Science*, **2020**,1-8(2020).
[15] Tanase C., Cosarca S., Muntean D., A critical review of phenolic compounds extracted from the bark of woody vascular plants and their potential biological activity. *Molecules*, **24**, 1182, 1-18(2019).
[16] Ahmad I., Khalique A., Qamar Shahid M., Rashid A. A., Faiz F., AsimIkram M., Ahmed S., Imran M., Khan A.M., Nadeem M., Afzal M. I., Umer M., Kaleem I., Shahbaz M., Rasool B., Studying the influence of apple peel polyphenol extract fortification on the characteristics of probiotic yoghurt. *Plants*, **9**, 77,1-15(2020).
[17] Koolaji N., Shammugasamy B., Schindeler A., Dong Q., Dehghani F., Valtchev P., Citrus peel flavonoids as potential cancer prevention agents. *Dev Nutr*,**4**, 1-20 (2020).
[18] Long X., Zeng X., Yan H., Xu M., Zeng Q., Xu C., Xu Q., Liang Y., Zhang J., Flavonoids composition and antioxidant potential assessment of extracts from Gannanzao Navel Orange (*Citrus sinensi*s Osbeck Cv. Gannanzao) peel. *Nat Prod Res*.,1–5(2019).
[19] Rafiq S., Kaul R., Sofi S., Bashir N., Nazir F., Ahmad Nayik G., *Citrus* peel as a source of functional ingredient: a review., *Journal of the Saudi Society of Agricultural Sciences*,**17**(4),351–358(2018).
[20] Zhang J., Wu Y., Zhao X., Luo F., Li X., Zhu H., Sun C., Chen K., Chemopreventive effect of flavonoids from Ougan (*Citrus reticulata*cv. Suavissima) fruit against cancer cell proliferation and migration. *J Funct Foods*, **10**, 511–519(2014).
[21] Nakajima A., Ohizumi Y., Potential benefits of nobiletin, a *citrus* flavonoid, against alzheimer's disease and parkinson's disease. *Int J Mol Sci*., **20**(14), 3380(2019).
[22] Ciumarnean L., Milaciu M. V., Runcan O., Vesa T. C., Rachis A. L., Negrean V., Perné M., Donca V. I., Alexescu T., Para I. and Dogaru G., The effects of flavonoids in cardiovascular diseases. *Molecules*, **25**, 4320, 1-18(2020).
[23] Jacob J.K., Hakimuddin F., Paliyath G. , Fisher H., Antioxidant and antiproliferative activity of polyphenols in novel high polyphenol grape lines. *Food Res Int*., **41**(4),419(2008) .
[24] Ergen I., Turgut B., Ilhan N., Comparison of the impact of epigallocatechin gallate and ellagic acid in an experimental cataract model induced by sodium selenite. *Int J Ophthalmol*., **10**(4), 499–506(2017).
[25] Gualdani R., Cavalluzzi M. M., Lentini G., Habtemariam S., The chemistry and pharmacology of *citrus* limonoids. *Molecules*, **21**, 1530,1-39(2016).
[26] Khoo H. E., Azlan A., Tang S. T., Lim S. M., Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutr Res*., **61**(1), 1-21(2017).
[27] Pietro D. P., Medeiros N.I., Vieira F.G.K., Fausto M.A., Bello-Klein A., Breast cancer in southern Brazil: Associationwith past dietary intake. *Nutricion Hospitalaria*, **22**,565-572 (2007).
[28] Castañeda-Ovando A., de Lourdes Pacheco-Hernández M., Páez-Hernández E, *et al*. Chemical studies of anthocyanins: a review. *Food Chem*., **113**(4), 859–871(2009).
[29] Lila M. A., Anthocyanins and Human Health: An *In Vitro* Investigative Approach. *Journal of Biomedicine and Biotechnology* , **5**, 306–313(2004).
[30] Issa N. K., Abdul Jabar R. S., Hammo Y. H., Kamal I. M., Antioxidant activity of apple peels bioactive molecules extractives. *Science and technology*, **6**(3), 76-88(2016).
[31] Sonia N.S., Mini C. , Geethalekshmi P.R., Vegetable peels as natural antioxidants for processed foods – A review. *Agricultural Reviews,* **37** (1), 35-41(2016).
[32] Hamid A. A., Aiyelaagbe O. O., Usman L. A., Ameen O. M., Lawal A., Antioxidants: Its medicinal and pharmacological applications. *Afr. J. Pure Appl. Chem.*, **4**, 142-153(2010).
[33] Aguiar J., Gonçalves J. L., Alves V. L. , Câmara J. S., Chemical fingerprint of free

polyphenols and antioxidant activity in dietary fruits and vegetables using a non-targeted approach based on QuEChERS ultrasound-assisted extraction combined with UHPLC-PDA. *Antioxidants***,** **9**, 305, 1-22(2020).

[34] Mokbel M. S. , Hashinaga, F. , Antibacterial and antioxidant activities of banana (*Musa*. AAA cv. Cavendish) fruits peel. *Am. J. Biochem. Biotech.*, **1**, 125 – 131(2005).

[35] Fatemeh S. R., Saifullah R., Abbas F. M. A. , Azhar M. E., Total phenolics, flavonoids and antioxidant activity of banana pulp and peel flours: influence of variety and stage of ripeness. *Int. Food Res. J.*, **19**, 1041 – 1046(2012).

[36] Friedmen, M., Chemistry, biochemistry and dietary role of potato polyphenols. *J.Agric. Food Chem.*, **45**, 1523 – 1540(1997).

[37] Kazuhiro N., Takayuki M., Tamaki H. , Hidenori, K., Antioxidative activity of bound form phenolics in potato peel. *J. Biosci. Biotechnol.Biochem.*, **70**,1489 – 1491(2006).

[38] Lewinsohn E., Sitrit Y., Bar E., Azulay Y., Ibdah M., Mair A., Yosef E., Zamir D. , Tadnor Y., Not just colours – carotenoid degradation as a link between pigmentation and aroma on tomatoes and watermelon fruits. *Trends Food Sci. Technol.*, **16**, 407 - 415(2005).

[39] Rimando, A. M. , Perkins – Veazie, P. M., Determination of citrulline in watermelon rind. *J. Chromatography*, 1, 196 – 200(2005).

[40] Agarwal M., Kumar A., Gupta R. , Upadhyaya, S., Extraction of polyphenol, flavanoid from *Emblica officinalis*, *Citrus limon*, *Cucumis sativus* and evaluation of their antioxidant activity. *Oriental J. Chem.*, **28**,993-998(2012).

[41] Zeyeda N. N., Zeitoun M. A. M., , Barbary, O. M., Utilisation of some vegetables and fruits waste as natural antioxidants. *Alex. J. Food Sci. Technol.*, **5**,1 -11(2008).

[42] Pallavi M., Ramesh C.K., Krishna V., Parveen S., *In vitro* antiproliferative and free radical scavenging activities in peels of citrus fruits.*Life Science Informatics Publications*, **4**(4), 293-304(2018).

[43] Baskar R., Dai J., Wenlong N., Yeo R., Yeoh, K.-W., Biological response of cancer cells to radiation treatment. *Front. Mol. Biosci*., 1- 24 (2014).

[44] Nguyen N. H., Ta Q. T. H., Pham Q. T., Luong T. N. H., Phung V. T., Duong T. , Vo V. G. , Anticancer activity of novel plant extracts and compounds from adenosmabracteosum (Bonati) in human lung and liver cancer cells. *Molecules*, **25**, 2912, 1-21(2020) a.

[45] Agarwal G., Carcache P.J.B., Addo E.M., Kinghorn A.D., Current status and contemporary approaches to the discovery of antitumor agents from higher plants. *Biotechnol. Adv*., **38**, 107337, 1-27(2020).

[46] Iqbal J., Abbasi B.H., Batool R., Mahmood T., Ali B., Khalil A.T., Kanwal S., Shah A., Ahmad R., Potential phytocompounds for developing breast cancer therapeutics: Nature's healing touch. *Eur. J. Pharmacol.*, **827**, 125–148(2018).

[47] Clere N., Faure S., Martinez MC, Andriantsitohaina R., Anticancer properties of flavonoids: roles in various stages of carcinogenesis. *Cardiovasc.Hematol. Agents Med. Chem*., **9**(2011).

[48] Tajaldini M., Samadi F., Khosravi A., Ghasemnejad A., Asad J., Protective and anticancer effects of orange peel extract and naringin in doxorubicin treated esophageal cancer stem cell xenograft tumor mouse model. *Biomedicine & Pharmacotherapy*, **121**, 109594(2020).

[49] Nguyen N.H., Nguyen T.T., Ma P.C., Ta Q.T.H., Duong T.-H., Van Giau V., Potential antimicrobial and anticancer activities of an ethanol extract from Boueamacrophylla. *Molecules*, **25**(8), 1996, 1-23(2020) b.

[50] Lee L., Huang Y., Hwang J., Lee A., Ke F., Huang C., Kandaswami C., Lee P., Lee M., Transinactivation of the epidermal growth factor receptor tyrosine kinase and focal adhesion kinase phosphorylation by dietary flavonoids: effect on invasive potential of human carcinoma cells. *Biochem Pharmacol.*, **67**(11), 2103–2114(2004) a.

[51] Liao C-Y., Lee C-C., Tsai C-C., Hsueh C-W., Wang C-C., Chen IH., Tsai MK., Liu M-Y., Hsieh A-T., Su K-J., *et al*. Novel investigations of flavonoids as chemopreventive agents for hepatocellular carcinoma. *Biomed Res Int.*, **2015**, 840542(2015).

[52] Yanez J., Vicente V., Alcaraz M., Castillo J., Benavente-Garcia O., Canteras M., Teruel J.A., Cytotoxicity and antiproliferative activities of several phenolic compounds against three melanocyte cell lines: relationship between structure and activity. *Nutr Cancer*, **49**(2), 91–199(2004).

[53] Günes-Bayir A., Kocyigit A., Güler E. M., *In vitro* effects of two major phenolic compounds from the family Lamiaceae plants on the human gastric carcinoma cells, *Toxicol. Ind.Health.*, **34**, 525-539(2018).

[54] Keta O., Deljanin M., Petković V., Zdunić G., Janković T., Živković J., Ristić-Fira A., Petrović I., Šavikin K., Pomegranate (*Punicagranatum L.*) peel extract: potential cytotoxic agent against different cancer cell lines. *Rec. Nat. Prod*., **14,** 5 , 326-339(2020).

[55] Sparg S., Light M. E., Staden V. J., Biological activities and distribution of plant saponins.*J.Ethnopharmacol.*, **94**, 219–243(2004).

[56] Wang Y. *et al*., Exploration of the correlation between the structure, hemolytic activity,

and cytotoxicity of steroid saponins. *Bioorg. Med. Chem.*, **15**, 2528–2532(2007).
[57] Lee K.-R. *et al*., Glycoalkaloids and metabolites inhibit the growth of human colon (HT29) and liver (HepG2) cancer cells. *J. Agric. Food Chem.*, **52**, 2832–2839(2004) b.
[58] Fekry M. I., Ezzat S.M., Salama M. M., Alshehri O. Y. , Al-Abd A. M., Bioactive glycoalkaloides isolated from *Solanum melongena* fruit peels with potential anticancer properties against hepatocellular carcinoma cells. *Scientific reports*, **9**,1746, 1-11(2019).
[59] Santos I. B. da S., Santos B. S. d., Oliveira J. R. S., Costa W. K., Nascimento da Silva A. Z., L. C., Ferreira M. R. A., Lermen V. L., Lermen M. S. B. de Sousa, Silva A. G. da, Ximenes R. M., Soares L. A. L., Paiva P. M. G., Lima V. L. de Menezes, Correia M. T. dos Santos, Silva M. V. da., Antioxidant action and *in vivo* anti-Inflammatory and antinociceptive activities of *Myrciaria floribunda* fruit peels: possible involvement of opioidergic System. *Advances in Pharmacological and Pharmaceutical Sciences*, **2020**, 1-11(2020).
[60] Malleshappa P., Kumaran R. C., Venkatarangaiah K., Parveen S., Peels of citrus fruits: a potential source of anti-inflammatory and anti-nociceptive agents.*Pharmacogn J*., **10**(6) Suppl:s172-s178(2018).
[61] Rajalakshmi P., Vadivel V., Brindha P., Investigation of *in vitro* antioxidant and anti-inflammatory activities of selected siddha polyherbal formulations. *Indian J of Pharmaceutical Education and Research*,**51**(4S), S747-S753(2017).
[62] Ekbote MT., Ramesh CK., Mahmood R., Thippeswamy BS., Veerapur V., Anti-inflammatory and analgesic activities of *Azimatetracantha*Lam leaves. *Journal of Pharmacy Research*, **3**(3),478-81(2010).
[63] Roy S.P., Niranjan C.M., Jyothi T.M., Shankrayya M.M., Vishawanath K.M., Prabhu K., *et al.*, Antiulcer and anti-inflammatory activity of aerial parts *Enicostemmalittorale* Blume.*Pharmacology*, **2**(4),369-373(2010).
[64] Amin B., Rachida A., Anti-inflammatory activity citrus essence (*C. Sinensisand C. aurantium*) local to chlef region (Algeria): *In vivo* study. *Journal of Biomolecular Research and Therapeutics*, **4**, 126(2015).
[65] Vanu M.R., Palanivelu S., Panchanatham S., Immunomodulatory and anti-inflammatory effects of *Semecarpusana cardium* Linn. Nut milk extract in experimental inflammatory conditions. *Biologica and Pharmaceutical Bulletin*, **29**(4),693-700 (2006).
[66] Othman R.A., Moghadasian M.H., Beyond cholesterol-lowering effects of plant sterols: Clinical and experimental evidence of anti-inflammatory properties. *Nutrition Reviews*,**69**(7), 371-82(2011).
[67] Kam P.C, Liew S., Traditional Chinese herbal medicine and anaesthesia. *Anaesthesia*, **57**(11), 1083-9(2002).
[68] Andrikopoulos N.K.,Kaloria A.C., Assimopolou N.A., Biological activity of some naturally occurring resins, gums and pigments against *in vitro* LDL oxidation. *Phytotherapy Research*.,**7**(5),501-507(2003).
[69] Rakholiya K., Kaneria M., Chanda S., Physicochemical and phytochemical analysis of different parts of Indian Kesar mango–a unique variety from Saurashtra region of Gujarat.*Pharmacogn J*.,**8**(5),502-506(2016).
[70] Kim H., Moon J.Y., Kim H., Lee D.S., Cho M., Choi H.K, *et al*. Antioxidant and antiproliferative activities of mango (*Mangiferaindica*L.) flesh and peel. *Food Chem*.,**121**(2),429-36(2010).
[71] Umamahesh K., Ramesh B., Kumar B. V., Reddy O. V. S., *In vitro* anti-oxidant, anti-microbial and anti-inflammatory activities of five Indian cultivars of mango (*Mangifera indica* L.) fruit peel extracts. *J Herbmed Pharmacol*., **8**(3), 238-247(2019).
[72] Nile S.H., Nile A.S., Keum Y.S., Total phenolics, antioxidant, antitumor, and enzyme inhibitory activity of Indian medicinal and aromatic plants extracted with different extraction methods. *3 Biotech*., **7**(1),76(2017).
[73] Knodler M., Conrad J., Wenzig E.M., Bauer R., Lacorn M., Beifuss U., et al., Anti-inflammatory 5-(11'Z-heptadecenyl)- and 5-(8'Z,11'Z-heptadecadienyl)-resorcinols from mango (*Mangiferaindica*L.) peels. *Phytochemistry*, **69**(4),988-93(2008).
[74] Ammar A.A., Turki M., Hammouda O., Chtourou H., Trabelsi K., Bouaziz M., Abdelkarim O., Hoekelmann A., Ayadi F., Souissi N. *et al*., Effects of pomegranate juice supplementation on oxidative stress biomarkers following weightlifting exercise. *Nutrients*, **9**, 819, 1-13(2017).
[75] Mastrogiovanni F., Mukhopadhya A., Lacetera N., Ryan M. T., Romani A., Bernini R., Sweeney T., Anti-Inflammatory effects of pomegranate peel extracts on in vitro human intestinal Caco-2 cells and ex vivo porcine colonic tissue explants. *Nutrients*, **11**(548),1-15(2019).
[76] Mastrogiovanni F., Bernini R., Basiricò L., Bernabucci U., Campo M., Romani A., Santi, L., Lacetera N., Antioxidant and anti-inflammatory effects of pomegranate peel extracts on bovine mammary epithelial cells BME-UV1. *Nat. Prod. Res*., **34**(10),1-17(2020).
[77] Zhang H., Tsao R., Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects.*Curr.Opi. Food Sci*., **8**, 33–42(2016).