Review

Fruit and vegetable peels: Paving the way towards the development of new generation therapeutics

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ABSTRACT: Cardiovascular diseases (CVDs), diabetes mellitus (DM), cancer, and thyroid abnormalities are major health problems prevalent around the world and are responsible for a large portion of morbidity and mortality out of health problems overall. Advances in genomics and proteomics in recent years have led to an explosion in the number of possible therapeutic targets and drug candidates through use of molecular approaches, chemical synthesis, traditional medicinal chemistry, and phyto-chemistry and through the exploration of novel herbal preparations. However, virtually none of these candidates are devoid of potential adverse drug reaction(s) or undesirable side effects. Therefore, the clear need is to look to alternative ways to develop novel drug candidates with fewer side effects and less cost. Interestingly, the last few years have seen an increase in the number of available reports on fruits and vegetable peels, and particularly on their biological activity, their content of different bioactive compounds, their chemical characterization, understanding of their structure-activity relationships, isolation and purification of commercially important chemicals without using high throughput techniques, *etc.* Therefore, research in the field of fruit and vegetable peels should present immense possibilities for drug discovery and development of cost-effective therapies that have fewer or practically no side effects. This virtual explosion of interest in fruit and vegetable peels as a source of medicinal and nutritional value has led to the present review.

Keywords: Cardiovascular problems, cancer, diabetes mellitus, thyroid problems, peels

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1. Introduction

Cardiovascular diseases including coronary heart disease (heart attacks), cerebrovascular disease, raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure, diabetes mellitus (both types 1 and 2), thyroid abnormalities (broadly hypo- and hyper-thyroidism), and cancer are among the most prevalent diseases around the world and are responsible for a large portion of morbidity and mortality out of health problems overall (*1-9*).

A vast body of literature is available on the possible therapeutic targets for those diseases, although many substances are either in clinical trials or used in practice (*10-37*). However, they have some major drawbacks including their high cost and adverse effects like cardiovascular events, cancer, aging, cardiac and renal toxicity, and increased oxidative stress (*38-51*). Oxidative stress is itself known to be a root cause for the progression and development of the diseases mentioned (*6*), and modern medicines should be designed in a way to maintain a healthy homeostasis between oxidants and antioxidants. As most herbal preparations are antioxidative in nature, they improve health directly by reducing oxidative stress (*6,52,53*). In fact, many herbal extracts are known to be antiperoxidative, anti-cancer, cardio-protective, anti-diabetic, and thyro-regulatory in nature (*3,4,54-58*). However, the identification of the plant(s) and its availability, precise chemical composition, dose, potential use for ailment(s), precise mechanism of action, unpredictable toxicity, and cost are major concerns that hinder the use of herbal preparations (*59*). That said, fruit and vegetable peels have advantages over other herbal extracts, as they are easily identifiable, commonly used by people, rich in various bioactive compounds, and some of their compounds have been characterized in terms of their chemical structures and biological properties through use of structure-activity relationships (SAR). Additionally, peels are usually considered waste, so they are obviously cost-effective (*60-64*).

Therefore, the present review has attempted to

assess the emerging potential of fruit and vegetable peels for use in developing new generation therapeutics.

2. Anti-peroxidative or radical-scavenging properties

Free radical production in any organism can either be accidental or deliberate. Free radicals have increasingly been accepted as commonplace and important biochemical intermediates, leading to these compounds being implicated in a large number of human diseases including cardiovascular problems, diabetes mellitus, cancer, thyroid disorders, and Alzheimer's disease (*6*).

Various fruit and vegetable peel extracts or compounds are known to be antiperoxidative in nature and their different *in vitro* or *in vivo* mechanism(s) have also been reported (Table 1). The antiperoxidative or radical-scavenging potential of the peel extracts from *C. sinensis*, *P. granatum*, *M. paradisiaca*, *C. vulgaris*, *C. melo*, and *M. indica* is well documented in both *in vivo* and *in vitro* models (*52,53,63-67*). In fact, the current authors have demonstrated that these peel extracts work mainly through the direct radical scavenging of various types of radicals in a dose-specific manner (*64*). Possible mechanism(s) of their antiperoxidative potential might be mediated *via* the presence of a variety of polyphenols and flavonoids in different concentrations. Specifically, *C. sinensis* was found to be an efficient scavenger for DPPH, singlet oxygen, and various peroxyradicals. *P. granatum* and *M. paradisiaca* were also found to be effective against all the aforementioned radicals and nitric oxide (NO) radicals as well, while *M. indica* was found to be effective only against peroxyradicals and *C. vulgaris* and *C. melo* were similarly found to be effective only against singlet oxygen and peroxyradicals. All of the aforementioned peels also have a minor influence on enzymatic and non-enzymatic oxidative defense, which includes catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH), particularly in the event of disease (*53,66*). Other citrus fruit peels including *C. reticulata* and *C. paradisi* are also known to have an antiperoxidative effect (*68,69*). Similarly, extracts of *P. liguralis* peels are reported to have considerable antioxidant activity, as represented by the trolox equivalent antioxidant capacity (TEAC) value, due to the presence of various antioxidative bioactive compounds, certainly indicating the importance of this peel as an alternative source of bioactive compounds (*70*). Peach, pear, and apple peels are also reported to have antioxidative potential according to various *in vitro* methods such as total radical-trapping antioxidative potential (TRAP) values, which also correlate with their polyphenolic content. Peels of those fruits have also been found to be antiperoxidative in hypercholesterolemic diet-fed animals (*71*). Pears and apples were further characterized by beta-carotene bleaching and NO and DPPH radical-scavenging potential (*60*). Peels from Red grape marc have also been found to be a radical quencher according to a beta-carotene bleaching assay (*72*). Solanum melongena is known to contain very strong antioxidants, including nasunin, and its antioxidative potential has been demonstrated using electron spin resonance spectrometric analysis, 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), spin trapping, hydroxyl (•OH) or superoxide anion radicals (O^{2-}) generated by a Fenton reaction, and hypoxanthine-xanthine oxidase systems (*73*). Both *S. melongena* L. and *C. annuum* L. peels are also reported to have *in vitro* antiperoxidative potential due to the presence of some other strong antioxidant compounds (*74*). *Solanum tuberosum* peel extract has also been found to have an antioxidative effect on erythrocytes and in rats with streptozotocin-induced diabetes (*75,76*). Jaffa grapefruit peels have been evaluated in DPPH and beta-carotene linoleate model systems and have been found to be radical scavengers *in vitro* (*77*). The peel extract of *L. siceraria* has also recently been reported to have antiperoxidative potential in both *in vitro* and *in vivo* studies; *in vitro* analysis demonstrated that this peel extract not only quenches DPPH radicals but also lowers hepatic lipid peroxidation values induced by CCl_4 and H_2O_2 (*62*). A parallel *in vivo* study on normal healthy and hyperthyroid mice further confirmed its antioxidative efficacy (*62*).

Table 1. Antiperoxidative potential of fruit and vegetable peels

Botanical name	English name	References
1. *Citrus sinensis*	Sweet orange	(*64-66*)
2. *Citrus reticulata*	Mandarin	(*68,149*)
3. *Citrus paradisi*	Jaffa grapefruit	(*68*)
4. *Musa paradisiaca*	Banana	(*52,64,65,94*)
5. *Citrullus vulgaris*	Watermelon	(*63,64,67*)
6. *Cucumis melo*	Melon	(*63,64,67*)
7. *Mangifera indica*	Mango	(*63,64,67,150,151*)
8. *Punica granatum*	Pomegranate	(*52,64,65,99,135*)
9. *Passiflora liguralis*	Sweet granadilla	(*153*)
10. *Legenaria siceraria*	Bottle gourd	(*62*)
11. *Solanum melongena* L.	Brinjal	(*73,74*)
12. *Solanum tuberosam*	Potato	(*75,76*)
13. *Capsicum annuum* L.	Sweet pepper	(*74*)
14. *Cydonia vulgaris*	Quince	(*154*)
15. *Pyrus malus*	Apple	(*60,71,133*)
16. *Pyrus pashia*	Pear	(*60,71*)
17. *Prunus persica*	Peaches	(*71*)

3. Cardiovascular protective effect

Many flavonoids and their glycosides present in herbal extracts are known for their cardiovascular regulatory properties (Table 2) and many are abundantly available in fruit and/or vegetable peels including rutin, isoquercetin, narirutin, narcissin, quercetin, kaempferol, luteolin, and apigenin are known to have a vasodilatory and hypotensive effect (*78-80*). Some of the flavonoids, such as quercetin and quercetin glycosides, are reported to have lipid-lowering and anti-atherosclerotic activity (*79,81-83*). In fact, hesperidin and naringin, both citrus

Table 2. Fruit and vegetable peels known for their cardiovascular effect

Botanical name	English name	References
1. *Citrus sinensis*	Sweet orange	(*52*)
2. *Citrus reticulata*	Mandarin	(*84*)
3. *Musa paradisiaca*	Banana	(*52*)
4. *Citrullus vulgaris*	Watermelon	(*65,118*)
5. *Cucumis melo*	Melon	(*65*)
6. *Mangifera indica*	Mango	(*52,115*)
7. *Punica granatum*	Pomegranate	(*52*)
8. *Citrus paradisi*	Jaffa grapefruit	(*77*)
9. *Pyrus malus*	Apple	(*60,71*)
10. *Pyrus pashia*	Pear	(*60,71*)
11. *Prunus persica*	Peaches	(*60*)

bioflavonoids also present in citrus fruit peels, exhibit biological and pharmacological properties, such as anti-inflammatory, lipid-lowering, and antioxidative behavior; all are related to cardiovascular health (*84,85*).

The mechanism(s) of the aforementioned effects may be explained by the fact that oxidative modification of low-density lipoproteins (LDL) by free radicals is an early event in the pathogenesis of atherosclerosis. The rapid uptake of oxidatively modified LDL *via* a scavenger receptor leads to the formation of foam cells. Oxidized LDL also has a number of other atherogenic properties. A number of mechanisms are likely to contribute to inhibition of LDL oxidation by flavonoids. Flavonoids may directly scavenge some radical species by acting as chain-breaking antioxidants (*86*). In addition, they may recycle other chain-breaking antioxidants such as α-tocopherol by donating a hydrogen atom to the tocopheryl radical (*87*). Transition metals such as iron and copper are important pro-oxidants, and some flavonoids can chelate divalent metal ions, hence preventing free radical formation.

A detailed *in vivo* study of *C. sinensis, P. granatum, M. paradisiaca*, *C. vulgaris*, *C. melo,* and *M. indica* peels in a diet-induced animal model of atherosclerosis revealed the anti-atherogenic potential of extracts. The study also revealed their direct benefit of maintaining cardiovascular health by positively influencing serum lipids (including total cholesterol, triglycerides, LDL-cholesterol, and VLDL-cholesterol), the atherogenic index, glucose, tissue lipid peroxidation, the serum level of creatinine kinase-MB enzyme, and histopathological alterations (*52,67*). The possible reasons for this beneficial role correlated with the presence of a variety of total flavonoids, phenolic compounds, and ascorbic acid content of the peel extracts (*66,67*). The aforementioned fruit peels are specifically known to contain various bioactive compounds that are already known for their cardiovascular or related benefits, including antiperoxidative, anti-inflammatory, and cardioprotective action. In brief, the protective effect of *C. sinensis* peels might be due to the presence of polymethoxylated flavones, *C*-glycosylated flavones, *O*-glycosylated flavones, flavonols, phenolic acids, nobiletin, hesperidin, and naringin (*88-92*). In *M. paradisiaca*, dopamine seems to be responsible as it is known to have strong antiperoxidative properties that are known to be associated with the amelioration of cardiovascular problem(s) (*6,93-97*). In *P. granatum*, some compounds are already known for their antiperoxidative and anti-inflammatory properties, including oleanolic, ursolic, and gallic acids, punicalagin, ellagitannin, ellagic acid, and catechin (*98-107*). Similarly, the anti-atherogenic activity of the peel extract of *M. indica* could be the result of the action of its rich polyphenolic content. Q 3-galactoside, Q 3-glucoside, and Q 3-arabinoside, gallic acid, and mangiferin are reported to have an antioxidative, anti-inflammatory, and cardioprotective role (*108-115*). The protective activity of *C. vulgaris* and *C. melo* peels mainly relates to their high content of citrulline, an essential amino acid that helps in nitric oxide synthesis that, in turn, enhances vasodilatation (*116-118*). Peels from Jaffa grapefruit (*C. paradisi*), pears, peaches, and apples were also evaluated for their possible cardiovascular benefits in hypercholesterolemic diet-fed animals. These peels increased plasma antioxidant capacity and improved plasma levels of different lipids. Further correlation studies revealed that the observed benefits of these peels might be mediated *via* the presence of total flavonoids, phenolics, phenolic acids, and dietary fiber at various levels of correlation (*77*).

Table 3. Anti-diabetic or gluco-regulatory potential of fruit and vegetable peels

Botanical name	English name	References
1. *Citrus sinensis*	Sweet orange	(*65-67,119*)
2. *Punica granatum*	Pomegranate	(*65,67*)
3. *Mangifera indica*	Mango	(*63*)
4. *Citrullus vulgaris*	Watermelon	(*63*)
5. *Solanum tuberosum*	Potato	(*75*)
6. *Legenaria siceraria*	Bottle gourd	(*62*)

4. Antidiabetic or gluco-regulatory potential of fruit and vegetable peels

Dietary antioxidant compounds such as bio-flavonoids may offer some protection against the early stage of diabetes mellitus and the development of complications (Table 3). Available reports describe the known mechanism(s) of bioflavonoids that are present in peels, such as hesperidin and naringin as are present in citrus fruit peels. These peels play an antidiabetic role in C57BL/KsJ-db/db mice *via* regulation of gluco-regulatory enzymes *i.e.*, they decrease the activity of glucose-6-phosphatase and phosphoenol pyruvate with a concomitant increase in the activity of hepatic glucokinase, increased hepatic glycogen content, and increased serum insulin along with a decrease in serum glucose concentrations (*80*).

C. sinensis and *P. granatum* peel extracts have also been found to be thyroid-stimulating in nature

when evaluated in normal healthy animals (*65*). Their antidiabetic potential was further confirmed by the experimentation using alloxan induced diabetes mellitus, hypercholesterolemic diet fed, and hyperthyroid animal models of study, which indentified the mechanism for the observed effects of *C. sinensis* peels and suggested that the antidiabetic potential of this peel extract might be mediated *via* antiperoxidation, α-amylase enzyme activity inhibition that is responsible for the conversion of complex carbohydrates to glucose, increased hepatic glycogen content, insulin-stimulating activity, and repair of secretory defects in β-cells (*53*). Inhibition of α-amylase enzyme activity by *Citrus sinensis* peel extract was also reported by other authors (*119*). *P. granatum* is suggested to have intrinsic antiperoxidative and hypoglycemic properties that may be attributed to some of its bioactive compounds, including oleanolic, ursolic, and gallic acids, punicalagin, ellagitannin, ellagic acid, and catechin (*98-107*). This protective effect was further correlated with the total phenolic and flavonoid compound content in the peels (*53*). However, *M. indica* and *C. vulgaris* have displayed neither any intrinsic hypoglycemic potential nor any antidiabetic potential in diabetic models (data not shown) but have been found to produce hypoglycemia in hyperlipidemia-induced diabetes (*67*). Therefore, these peel extracts may work *via* gluconeogenesis or glycogenolysis or glucose uptake in hypercholesterolemic animals. Therefore, it seems that these peels may be beneficial in obesity induced type 2 diabetic condition or in metabolic syndrome. Antidiabetic role of potato or *S. tuberosum* peels against streptozotocin induced diabetic model was also reported where, reversal in almost all the diabetic changes including serum glucose, body weight, polydipsia, polyuria, elevated activity of serum transaminases (ALT and AST) and hepatic MDA levels, and reduced glutathione (GSH) was observed (*75*). However, the plausible mechanism for this antidiabetic effect has not been completely elucidated but antiperoxidative potential was presumably a major contributing factor to the effect observed. Similarly, the peel extract of *L. siceraria* has been found to cause hypoglycemia in normal healthy and hyperthyroid mice. The hypoglycemic potential observed might be the outcome of thyroid and glucose-6-phosphatase inhibitory activity of the peel extract (*62*).

5. Thyro-regulatory potential

Some plant compounds are already known to influence the thyroid hormone homeostasis at various levels, including that of binding of TSH-receptor, thyroid-iodide transport and conversion of T_4 to T_3 (*120*). However, few reports (Table 4) have demonstrated the thyro-regulatory potential of fruit and vegetable peels (*52*,*53*,*62-67*). Peels from *C. sinensis* and *M. paradisiaca* have been found to inhibit the thyroid. Where, reduction in both the thyroid hormones was observed, in response to either of the peel extract. Therefore, it was suggested that both *C. sinensis* and *M. paradisiaca* might be inhibiting thyroid hormones not only at glandular level, but also at the level of peripheral conversion of T_4 to T_3. The antithyroidal role of *C. sinensis* might be mediated through the inhibition of thyroid peroxidase (TPO); the key enzyme in thyroid hormone biosynthesis, as it contains the phenolic compound naringin which inhibits the activity of TPO (*121-123*). Similarly, the antithyroidal role of *M. paradisiaca* might be mediated by its high dopamine content, which is already known to inhibit the thyroid as previously indicated (*94*,*124*,*125*).

The peel extracts of *M. indica*, *C. vulgaris*, and *C. Melo* were found to be thyro-stimulatory in nature. This thyroid stimulatory nature was further confirmed by a study of rats with chemically-induced hypothyroidism in which the administration of test peel extracts restored the serum levels of two thyroid hormones to normal in hypothyroid animals (*63*). These results clearly demonstrated the role the aforementioned peel extracts had in ameliorating hypothyroidism. An increased level of both thyroid hormones T_3 and T_4 demonstrated the thyroid stimulatory potential of these peel extracts on both the glandular level (the only source for T_4 synthesis) and at the level of peripheral monodeiodination of T_4, the main source of T_3.

Thus far, the mechanism for the effect(s) observed may relate to the presence of various small polyphenolic molecules that might play a major role in thyroid stimulatory activity, as they are already reported to influence thyroid hormone metabolism at genomic level. For instance, they increase the activity of the type 2 iodothyronine deiodinase gene (*126*). Secondly, other mechanisms are also possible, such as TPO stimulation, enhanced glandular functionality, and 5'-deiodinase activity, and could not be ruled out by these studies.

Table 4. Influence of fruit and vegetable peels on thyroid status

Botanical name	English name	Nature	References
1. *Citrus sinensis*	Sweet orange	Thyroid-inhibiting	(*65*,*66*)
2. *Musa paradisiaca*	Banana	Thyroid-inhibiting	(*65*)
3. *Legenaria siceraria*	Bottle gourd	Thyroid-inhibiting	(*62*)
4. *Citrullus vulgaris*	Watermelon	Thyroid-stimulating	(*63*)
5. *Cucumis melo*	Melon	Thyroid-stimulating	(*64*)
6. *Mangifera indica*	Mango	Thyroid-stimulating	(*63*)

6. Anticancer potential

Cancer is one of the most devastating diseases for which various remedies have been reported, but development of suitable therapeutics to treat this disease is still a major challenge for biomedical professionals. In the search for novel therapies and exploration of hitherto unknown compounds with anticancer potential, some reports have described herbal preparations including fruit and vegetable peels (Table 5) (*127-132*). A few important biochemical *in vitro* studies using different cancer cell lines and *in vivo* studies have revealed the potential some fruit peels have to combat variety of cancers, including cancer of the liver, colon, breast, and lung. Peels from different varieties of apples (Rome Beauty, Idared, Cortland, and Golden Delicious) are reported to have an antiproliferative effect (*130*). Golden delicious apple peels have been reported to inhibit the cell proliferation of HepG2 human liver cancer cells and MCF-7 human breast cancer cells (*133*). Some of the active principles present in these peels, such as quercetin and quercetin-3-*O*-beta-D-glucopyranoside, have been found to be responsible for the anticancer activity observed (*130*,*134*). The anticancer effect(s) observed might be mediated *via* inhibition of NF-kappa B activation (*131*). Some of the triterpenoids are also present in apple peels, including 2 alpha-hydroxyursolic acid, 2 alpha-hydroxy-3 beta-{[(2E)-3-phenyl-1-oxo-2-propenyl]oxy}olean-12-en-28-oic acid, 3 beta-trans-*p*-coumaroyloxy-2 alpha-hydroxyolean-12-en-28-oic acid, and 2 alpha-hydroxyursolic acid, and are known to possess anticancer potential *via* the inhibition of NF-kappa B activation (*134*). Similarly, peels of *Punica granatum* are also thought to have an anticancer effect in inflammation-associated cancers (*135*). Different *Citrus* varieties including *C. reticulata*, *C. unshiu*, and *C. natsudaidai* are known to prevent tumorigenesis (*136,137*). *C. reticulata* peels have displayed potent tumor-suppressing activity in SNU-C4 human colon cancer cells; the mechanism for this is believed to be *via* the up-regulation of the pro-apoptotic gene *Bax* and apoptotic gene *caspase-3* along with a concomitant decrease in the expression of the anti-apoptotic gene *bcl-2* (*138*).

The peel extract of *C. natsudaidai* has also been demonstrated to act on tumors in B-16 mouse melanoma and human lung carcinoma cells; it is theorized to contain hydrophobic antitumor compounds (*137*). In fact, 78 species of the genus *Citrus* are known to inhibit the Epstein-Barr virus early antigen (EBV-EA) activation (responsible for some cancers, including Burkitt's lymphoma) induced by 12-*O*-tetradecanoylphorbol 13-acetate (TPA); this serves as a useful screening method for anti-tumor promoters and further underscores the importance of peels in the development of potential anti-tumor therapies (*139*).

Isolated fractions of *D. kaki* (persimmon) peels have potent cytotoxic activity against human oral squamous cell carcinoma cells (HSC-2) and human submandibular gland tumor (HSG) cells (*140*). Interestingly, these fractions also had activity to reverse multiple drug resistance (MDR), further encouraging research on persimmon peels in the prevention and treatment of cancers as MDR is a frequently occurring event in most of the available cancer therapies (*140*). Similarly, cytotoxic and MDR reversal activity were also reported in response to treatment with Feijoa peel extract (*141*).

7. Active principles available in peels and their potential health benefits

Various compounds are present in both vegetable and fruit peels and are known for their different biological activities; these compounds are thought to be the active principles in these peels (Table 6). Different species of *S. melongena* contain various anthocyanins such as delphinidin 3-(*p*-coumaroylrutinoside)-5-glucoside (nasunin), delphinidin 3-rutinoside, delphinidin 3-glucoside, and petunidin 3-(*p*-coumaroylrutinoside)-5-glucoside (petunidin 3RGc5G). These compounds are all reported to have a varying degree of radical-scavenging potential. Delphinidin 3RGcaf5G is reported to have the highest level of radical-scavenging activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and linoleic acid radical systems, followed by nasunin and petunidin 3RGc5G, in that order (*73,142*). Interestingly, an *ex vivo* angiogenesis assay using a rat aortic ring revealed the antiangiogenic and antioxidative potential of nasunin (*78*). Similarly, delphinidin-3-rutinoside from *S. melongena* and delphinidin-3-*trans*-coumaroylrutinoside-5-glucoside from *C. annuum* L. are also reported to

Table 5. Fruit and vegetable peels known for their anticancer efficacy

Botanical name	English name	References
1. *Pyrus malus*	Apple	(*130,131,133,134*)
2. *Punica granatum*	Pomegranat	(*135*)
3. *Solanum lycopersicum*	Tomato	(*155*)
4. *Citrus reticulata blanco*	Mandarin orange	(*138*)
5. *Citrus unshiu*	Mikan	(*136,137*)
6. *Citri Reticulatae Viride*	Green Tangerine Orange	(*136,137*)
7. *Citrus natsudaidai*	Japanese summer grape fruit	(*137*)
8. *Diospyros kaki*	Persimmon	(*140*)
9. *Feijoa sellowiana*	Feijoa	(*141*)

Table 6. Active principles isolated from fruit and/or vegetable peels and known for their various biological properties

Name	Source	Biological activity	References
1. Different varieties of delphinidin anthocyanins, delphinidin-3-rutinoside, nasunin	*Solanum melongena*	Antioxidant	(*73,74,78,142*)
2. Flavonoids including quercetin-3-*O*-beta-D-glucopyranoside, quercetin-3-*O*-beta-D-galactopyranoside, quercetin, (−)-catechin, (−)-epicatechin, quercetin-3-*O*-alpha-L-arabinofuranoside, 2 alpha-hydroxyursolic acid	*Pyrus malus*	Anticancer	(*61,130,134*)
3. Various triterpenoids including ursolic acid, 3 beta-*trans*-*p*-coumaroyloxy-2 alpha-hydroxyolean-12-en-28-oic acid, (−)-epicatechin, procyanidin B2, chlorogenic acid, and catechins and flavonol glycosides, especially rutin	*Pyrus malus*	Antioxidant	(*61,130,134*)
4. Epicatechin, gallic, and *p*-coumaric acids	*Diospyros kaki* *Pyrus malus*	Antiatherosclerotic	(*143*)
5. Caffeic, *p*-coumaric, and ferulic acids	*Pyrus malus* *Pyrus pashia* *Prunus persica*	Lipid lowering	(*144,148*)
6. Mangiferin, penta-*O*-galloyl-glucoside, gallic acid, methyl gallate, quercetin *O*-glycosides, kaempferol *O*-glycoside, xanthone *C*-glycosides, mangiferin, isomangiferin, gallotannins	*Mangifera indica* L.	Antioxidant	(*150,151*)
7. Resorcinols including 5-(11'Z-Heptadecenyl)-resorcinol, 5-(8'Z, 11'Z-Heptadecadienyl)-resorcinol	*Mangifera indica* L.	Anti-inflammatory	(*152*)
8. Fatty acid esters of hydroxybenzoic acid, fatty acid esters of hydroxybenzaldehyde, glucosides of aromatic acids, chlorogenic acids, flavonols, and benzylamine	*Cydonia vulgaris*	Antioxidant	(*154*)
9. Xyloglucan (carbohydrate)	*Passiflora liguralis*	Antioxidant	
10. Flavanon glycosides hesperidin and naringin aglycones hesperetin and naringenin	Some *Citrus* fruits	Antioxidant	(*144,148*)
5-Hydroxy-3,6,7,8,3',4'-hexamethoxyflavone	*Citrus sinensis*	Anticancer	(*136,145*)
11. Cyclonatsudamine A	*Citrus natsudaidai*	Vasodilatation	(*146*)
12. Naringin, naringenin, hesperidin, hesperetin, rutin, nobiletin, and tangeretin	Some *Citrus* fruit peels	NO radical inhibition	(*149*)
13. Delphinidin-3-*trans*-coumaroylrutinoside-5-glucoside	*Capsicum annuum* L.	Antioxidant	(*74*)
14. Lycopene and carotenoids	*Solanum lycopersicum*	Cancer prevention	(*155*)
15. Hesperidin	*Citrus unshiu*	Decreased plasma triglycerides	(*148*)
16. Auraptene and umbelliferone	*Citrus natsudaidai*	Anticancer	(*136*)

be antiperoxidative according to two different *in vitro* antioxidant capacity assessment assays (*74*). Similarly, apple peels contain a number of major flavonoids, including quercetin-3-*O*-beta-D-glucopyranoside, quercetin-3-*O*-beta-D-galactopyranoside, and trace amounts of quercetin, (−)-catechin, (−)-epicatechin, and quercetin-3-*O*-alpha-L-arabinofuranoside (*130*). Among the compounds isolated, quercetin and quercetin-3-*O*-beta-D-glucopyranoside had potent antioxidative and antiproliferative activity against HepG2 (liver) and MCF-7 (breast) cancer cells, while caffeic acid, quercetin, and quercetin-3-*O*-beta-D-arabinofuranoside, all phenolic compounds, also had antioxidant activity (*134*). Interestingly, most of the flavonoids and phenolic compounds tested were found to be stronger antioxidants when compared to ascorbic acid and might be directly responsible for the antioxidative and antiproliferative activity of apple peels. The presence of triterpenoids, including 2 alpha-hydroxyursolic acid and ursolic acid, in apple peels also makes them a potent cytotoxic or anticancer agent, as evidenced by their inhibitory activity against four tumor cell lines (HL-60, BGC, Bel-7402, and Hela) (*61*). These compounds have anticancer activity *via* inhibition of NF-kappa B activation. Interestingly, structure-activity relationships (SAR) revealed that these triterpenes possess two hydrogen bond-forming

groups (an H-donor and a carbonyl group) at positions 3 and 28 with cytotoxic activity. The configuration at C-3 was found to be important for anticancer activity, as introduction of an amino group was found to greatly increase cytotoxicity. Other evidence has also confirmed the importance of the C-3 and 28 positions, *e.g.* a 3 beta-amino derivative had 20 times the potency of its parent ursolic acid and 28-aminoalkyl dimer compounds had selective cytotoxicity (*61*).

The peels of persimmons and apples have also been recommended as part of an antiatherosclerotic diet due to their rich amounts of total, soluble, and insoluble dietary fiber, total phenols, epicatechin, and gallic and *p*-coumaric acids along with concentrations of Na, K, Mg, Ca, Fe, and Mn (*143*).

The different active components isolated from citrus fruit peels are also known for their various health benefits and disease protection, including antiperoxidative and anticancer activity, vasodilatation, decreased serum triglycerides, and improved cardiovascular health (*144-148*). Caffeic acid, *p*-coumaric acid, ferulic acid, and *p*-hydroxybenzoic acid isolated from *C. unshiu* Marc. peels had antioxidative or radical-scavenging properties as represented by trolox equivalent antioxidant capacity (TEAC) values. Similarly, hesperidin isolated from the same citrus variety was found to decrease the level of serum triglycerides (*144,148*). A polymethoxyflavone compound, 5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone (5-OH-HxMF), from the sweet orange (*C. sinensis*) is found exclusively in the *Citrus genus* and known for its anticancer and anti-inflammatory potential according to 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), which lead to tumor progression, in mouse skin (*145*). Pre-treatment with a topical application of 5-OH-HxMF has been found to inhibit the TPA-induced nuclear translocation of nuclear factor-kappa B (NF-kappa B) subunit and DNA binding by blocking phosphorylation of inhibitor kappa B (IkappaB) alpha and p65 and subsequent degradation of IkappaB alpha (*145*). Another study also suggested the potential of OH-HxMF to inhibit 7,12-dimethylbenz[a] anthracene/TPA-induced skin tumor formation, as evidenced by a reduction in tumor incidence and tumor multiplicity of papillomas at 20 weeks (*136*). Because of its anti-inflammatory and anti-tumor properties, 5-OH-HxMF may prove to be a novel functional agent to prevent inflammation-associated tumorigenesis (*145*). A novel compound, cyclonatsudamine A, was isolated from *C. natsudaidai* and evaluated for its vasodilatory potential in a rat aorta model with norepinephrine-induced contractions. The mechanism of vasodilatation was presumably mediated by increased NO release from endothelial cells (*146*).

In fact, some citrus fruit peel extracts have been reported to have varying degrees of NO radical-scavenging activity, and these levels have been further correlated with the content of some flavonoids, including naringin, naringenin, hesperidin, hesperetin, rutin, nobiletin, and tangeretin (*149*). *M. indica* peels contain compounds such as quercetin *O*-glycosides, kaempferol *O*-glycoside, xanthone *C*-glycosides, mangiferin, and isomangiferin that may serve as natural antioxidants or functional food ingredients (*150*). Other components, including mangiferin, penta-*O*-galloyl-glucoside, gallic acid, and methyl gallate, are already reported to scavenge DPPH radicals, suggesting radical-scavenging activity (*151*). Similarly, two other compounds, 5-(11'Z-heptadecenyl)-resorcinol and 5-(8'Z,11'Z-heptadecadienyl)-resorcinol, are also reported to exhibit potent cyclooxygenase-1 (COX-1) and COX-2 inhibitory activity (*152*). Understanding structure-activity relationships revealed that the degree of unsaturation in the alkyl chain plays a key role in this COX inhibitory activity (*152*). In a TEAC assay system, an unknown polysaccharide xyloglucan from *Passiflora liguralis* or granadilla fruit peels was also reported to have antioxidative potential (*153*). Reports on assessing the capacity to scavenge the 2,2'-diphenyl-1-picrylhydrazyl (DPPH) radical and anion superoxide radical and to induce the reduction of Mo(VI) to Mo(V) indicated that various chlorogenic acids and the flavonols isolated from the peels of *Cydonia vulgaris* have antioxidative and radical-scavenging properties greater than those of alpha-tocopherol and ascorbic acid (*154*). Tomato consumption is associated with a lower incidence of upper aerodigestive tract and prostate cancers due to presence of carotenoids, lycopene, and/or beta-carotene, but interestingly the content of these compounds is higher in peels than in other parts of the fruit (*155*). In fact, an *in vitro* digestion model using human intestinal cells (Caco-2) revealed that tomato paste enriched with 6% peel increased lycopene absorption into intestinal cells 75% and beta-carotene absorption 41%, clearly demonstrating the important role that active principles present in peels might play in cancer prevention (*155*).

8. Future scenario

Reviewing all of the findings on fruit and vegetable peels leads to the conclusion that fruit and vegetable peels have immense potential as novel and promising therapies against the most prevalent diseases, *i.e.*, cardiovascular problems, diabetes mellitus, thyroid abnormalities, and various cancers.

Interestingly, most peels are considered to be waste and are believed to adversely affect the cleanliness of urban areas, so their utilization in pharma or nutraceuticals will certainly offer the potential for cost-effective new generation therapeutics and also enhance the value of fruits and vegetables. As oxidative stress is one of the major factors responsible for various diseases and tissue damage, the presence of strong antioxidants in peels suggests a reduced likelihood of potential drug

toxicity or adverse drug reaction(s). However, well planned pre-clinical studies exploring toxicity and efficacy evaluations that provide an understanding of molecular pathways of the biological effects observed are still needed before any clinical trials can be conducted.

Based on the available literature, evidence, and first-hand experience working in this field, the current authors are quite optimistic that the path from fruit and vegetable peels used in the laboratory to peels available on the market will only take a few more years; soon, they may serve as new generation therapeutics to treat cancer, cardiovascular diseases, diabetes mellitus and thyroid abnormalities.

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