Utilisation of Bioactive Compounds from Agricultural and Food Waste

Nutraceuticals

Utilisation

Cosmeceuticals

Pharmaceuticals

Editor: **Quan V. Vuong**

Utilisation of Bioactive Compounds from Agricultural and Food Waste

Utilisation of Bioactive Compounds from Agricultural and Food Waste

Editor

Quan V. Vuong

School of Environmental and Life Sciences
University of Newcastle, Australia

Preface

World food production has increased significantly over the last century largely due to the rise in population and consumer demand for food variation. Increase in food production has resulted in generation of high quantities of waste from the food production chain. Approximately 50 per cent of food from 'farm to table' is wasted. This is both a national and global problem because of the numerous risks caused by food waste to humans, animals and the environment.

Waste generated from agriculture and food production is considered as general waste because of its limited utilisation and low economic value. The large quantity of waste generated annually from agricultural and food production requires billions of dollars to be spent on agricultural and food waste treatment. Numerous studies undertaken on food waste reveal that it is a rich source of bioactive compounds, which can be extracted and isolated for further utilisation in the food, cosmetic and pharmaceutical industries.

Utilisation of bioactive compounds isolated from food waste not only reduces the risks and costs of waste treatment, but also adds more value to agricultural and food production. Information on different aspects of waste bioactive compounds proves useful for students, academics, researchers and professionals engaged in food science and the food industry. This book was developed with the aim of providing comprehensive information related to extraction and isolation of bioactive compounds from agricultural and food waste for utilisation in the food, cosmetic and pharmaceutical industries.

The topics range from bioactive compounds and potential health benefits, bioactive compounds in waste, techniques used to analyze, extract, isolate and encapsulate these compounds to several specific examples for potential utilisation of waste generated by the agricultural and food industry, such as rice, oil, wine and juice production. This book also discusses the potential of bioactives isolated from waste for re-use in important applications. It may be noted that the book covers only the main aspects of utilisation of bioactive compounds derived from plant waste materials, not from animal or marine materials. In addition, utilisation of by-products of agriculture and food produce is a complex issue. Although this book cannot cover the entire spectrum of utilisation of food waste, it is expected that the readers will find the information useful for their related works.

This book is an excellent compilation of knowledge gleaned by world experts, working on food waste and bioactive compounds. I would like to acknowledge the efforts of the authors in making invaluable contribution to this book. I am grateful to

the reviewers for their commitment to improving of the quality of this book. A word of thanks go to my wife, son and daughter for their encouragement. Finally, I would like to thank the CRC Press for publishing this book.

Quan V. Vuong

University of Newcastle Brush Road,
Ourimbah, NSW 2258 Australia
E-mail: vanquan.vuong@newcastle.edu.au

Content

CHAPTER 1

Bioactive Compounds in Agricultural and Food Production Waste

Nenad Naumovski,[1,*] *Senaka Ranadheera,*[2] *Jackson Thomas,*[3]
Ekavi Georgousopoulou[1] and *Duane Mellor*[1]

Introduction

The use of natural products from plants and foodstuffs as medicines or as a part of the medicinal approach has been recorded since ancient times. These medicines constituted key components of *traditional medicines* in the form of extracts, powders, potions and oils. However, they relied on combination of very complex and matrix-imbedded combinations of compounds, rather than on *pure* and individual compounds themselves. Today the pure components of these compounds are products predominantly identified as *secondary plant metabolites*. Interest in these compounds as potential drug-leads could be incorporated in new aspects of pharmaceutical design and as such pose significant new areas of development. This is mainly due to their very diverse structure when compared to the standard combinatorial chemistry, which allows the discovery of predominately low-molecular-weight lead compounds. From this perspective, current *modern-medicine* can be identified as having its own foundation based on the more traditional medicine approach (Naumovski 2015).

Today's society is described as one of an ageing population, predominantly due to the very large proportion of baby boomers (born after the Second World War) that are now approaching their *third age* of life, with the highest life expectancy ever. These trends are also seen globally in the developed and some developing countries. It is therefore expected that the new structure of the society will mainly be composed

---

[1] Discipline of Nutrition and Dietetics, Faculty of Health, University of Canberra, Locked Bag 1, Canberra, ACT, 2601, Australia. E-mail: Ekavi.Georgousopoulou@canberra.edu.au; duane.mellor@canberra.edu.au

[2] Advanced Food Systems Research Unit, College of Health & Biomedicine, Victoria University Werribee, VIC 3030, Australia. E-mail: Senaka.Ranadheera@vu.edu.au

[3] Jackson Thomas, Discipline of Pharmacy, Faculty of Health, University of Canberra, Locked Bag 1, Canberra, ACT, 2601, Australia. E-mail: Jackson.thomas@canberra.edu.au

* Corresponding author: nenad.naumovski@canberra.edu.au

of retired individuals or close to their retirement. Although the initial stage of the *third age* is commonly accepted to be relatively healthy and active, the last two-thirds are commonly burdened with increased incidence of illnesses, such as cardiovascular disease (WHO 2014), cognitive decline (Kumar et al. 2015) and various types of cancer (Cragg and Newman 2005). Demographic changes based on the age of the individual are responsible for development and re-design of new foods and functional foods to meet the new health and lifestyle challenges. Therefore, it is not surprising that the search for potential *functional foods* and *natural supplements* that can potentially delay the onset of these diseases (and associated ones) is on the increase both from the viewpoint of the consumer and the manufacturer (Covolo et al. 2013). Importantly, dependence on the use of these natural products (and their derivatives) can not only be seen from the specific age time-frame, but rather be viewed independent of the cross-cultural and geographical needs.

In addition to the increased proportion of society comprising an ageing population, there is a steady and consistent increase in the world population overall. This leaves humanity facing formidable challenges in securing adequate food sources for the well-being of the overall population (Sutovsky et al. 2016). Food waste reduction and reutilisation can been seen as the single and most easily approachable method to address issues of food security and health. The lowering of the traditionally seen food waste, such as usable but unused component of the food source, can effectively increase food usability (Godfray et al. 2011, Tilman et al. 2011). In addition, the use of non-usable food products commonly seen as the leftover of the primary food production, can also prove a significant source of bioactive compounds and as such, potentially reduce the burden on the primary food product itself. In 2011, the Food and Agriculture Organisation (FAO) identified that every year one-third of the world's food produced for human consumption is wasted (FAO 2011). This report specifically focuses on the *grown-but-not-eaten* foods and although it emphasizes the importance of food losses to combat hunger, raise income and improve the food security in some of the poorest countries, it points to the missed opportunity to improve global food output and utilisation.

Currently, the increased global need is for reduction of food waste from the socio-economic perspective and from all aspects of extraction and re-utilisation into the food system. This must be seen from the perspective of the single identifiable compound and also from the cocktail of compounds that can target increased health response. Therefore, the main aim of this chapter is to provide introduction to the current sources of food waste from agricultural production and to identify some of the most important classes of bioactive compounds found in the food waste. In addition, the potential significance of these compounds in use in today's nutraceutical industry will also be discussed briefly.

Sources of Agricultural and Food Production Waste

In general, *food waste* includes products that are not used, but are directly related to human consumption (FAO 2011). As such, the division can be made in five very broad systems boundaries (Table 1). Although not included in the strict definition of food waste, the use of *leftovers* of agricultural food production must be taken into account. Therefore, from the food industry perspective, waste can be derived from

Table 1. Identifiable 'Five system boundaries' of food waste (Adapted from FAO 2011).

System boundary	Examples of potential food losses
Agricultural production	Mechanical damage, spillage during harvesting, fruit picking
Post-harvest handling and storage	Spillage and degradation during handling, storage and transport
Processing	Industrial or domestic processing
Distribution	Market systems
Consumption	During consumption at the household level

raw vegetable and animal material processing during edible food material production (Baiano 2014). Interestingly, the food industry itself produces a significant amount of food waste, with the highest amounts being produced during the handling of fruit and vegetables, followed by milk, meat, fish and wine food productions (FAO 2011, Baiano 2014).

A large majority of the food industry's waste products contain potentially marketable bioactive compounds that are normally present in foods and associated products. Although interest in these compounds was reported since several decades, it is only recently that significant attention has been channelled towards utilisation and extraction of these bioactives from industry waste. Therefore, the new emerging aim of the food industry is to completely exploit the high value components, such as macronutrients (proteins and carbohydrates) and secondary plant metabolites, such as phytochemicals that contain potential nutraceutical-related properties.

Bioactive Compounds from Food Waste

It is well established that food, nutrition and pharmaceutical industries have a significant number of overlapping interests and areas of research. Since the rise of the term *nutraceuticals*, the search for natural compounds in the form of plant extract or as single compounds with beneficial health effects has risen exponentially and become a lead topic of many research laboratories around the globe (Naumovski 2015).

The term *bioactive compounds* is loosely used in today's literature despite the consensus in terminology defining it as the majority of non-nutritive compounds present in foods with the strong potential to improve human health (Biesalski et al. 2009). Interestingly, the use of non-nutritive compounds raises a query that is arguable, as some of these compounds can play a major role in nutrition and human health (Bernhoft 2010). In addition, minerals and vitamins are active components of plants and can induce beneficial and toxicological effects when ingested in relatively large quantities and over prolonged periods of time. However, when discussing the bioactives as a separate entity of compounds, these compounds must be produced as secondary plant metabolites (Cragg and Newman 2005, Biesalski et al. 2009).

Secondary plant metabolites (Fig. 1) are exceptionally diverse compounds, both structurally and chemically, and are quite often localised in specialised plant cells. These compounds are not directly required for the plant metabolism (such as photosynthetic or respiratory metabolism) but rather, their importance is sought in the
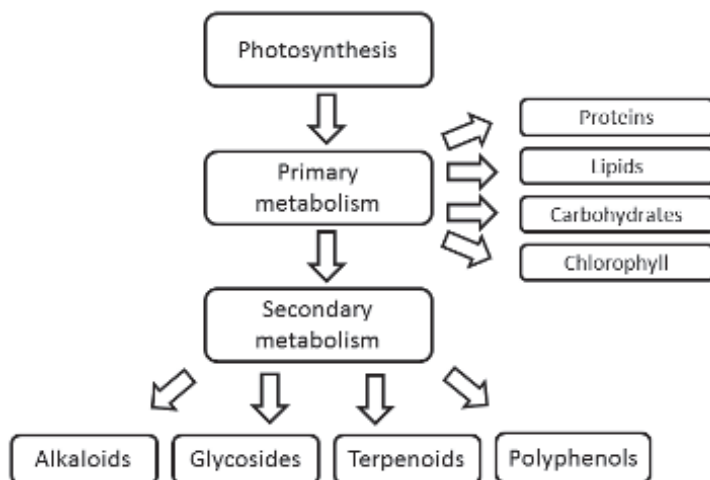
Figure 1. Brief outline of primary and secondary plant metabolites.

plant's survival in the environment. As such, their accumulation is associated with the developmental stages of the plant itself and can provide defensive (against parasites or competing plants) signalling (attraction to pollinating insects) and overall protective support to the plant (oxidant protection). Additionally, the pattern of distribution of these compounds is very diverse between the plant organs and organelles and also between the individual and different plant populations (such as same plant species, but from different geographical positions) (Lattanzio 2013).

The classification of plant secondary metabolites is commonly based on the biosynthetic route or structural features (Lattanzio 2013). However, these metabolites can also be viewed from the basis of clinical function related to their pharmacological effect and botanical approach considering their families (Cragg and Newman 2013, Naumovski 2015). Alkaloids and glycosides are amongst the important categories that are currently attracting a significant amount of research in relation to their recovery from industrial food waste sources—terpenoids and polyphenols (for nutraceutical development).

Structure, Classification and Occurrence of Bioactives in Food Sources

Alkaloids

Alkaloids are natural nitrogen-containing organic compounds with tremendous biological activities (Shi et al. 2014). These compounds are efficiently biosynthesized from amino acids, such as tyrosine (Evans and Mitch 1982) or from amination and transamination reactions (Aniszewski 2015). The boundary between alkaloids and other nitrogen-containing natural compounds is yet to be defined. However, in addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulphur and rarely other elements, such as chlorine, bromine and phosphorus (Kabera et al. 2014). The

majority of alkaloids are found in higher plants as secondary metabolites, especially in dicots while a few exist in the lower plants (Shi et al. 2014). Certain fungi, such as *Claviceps*, *Penicillium*, *Rhizopus* and *Aspergillus* (Dembitsky 2014) and bacteria including genus *Streptomyces* (Zotchev 2013) also contain natural alkaloids. Naturally-occurring plant alkaloids, in particular the alkaloids present in herbal medicinal plants, have been used in therapeutic application for centuries due to their wide range of pharmacological activities, including potential anti-inflammatory effect, antibacterial and antiviral effects, antimalarial, anticancer activity, hypoglycaemic effects, with positive effects on the central nervous system (Shi et al. 2014, Pereira et al. 2016) and adrenergic (stimulant) activity to promote weight loss (Fugh-Berman and Myers 2004). Thus alkaloids may also contribute to increased perception of flavor, taste and quality of fruits and vegetables (He et al. 2011).

At present more than 12,000 different natural compounds and their derivatives are recognized as alkaloids and their classification is challenging due to their great structural diversity (Hesse 2002, Chowański et al. 2016). Alkaloids can be classified broadly in terms of (1) biological and ecological activity, (2) relation to chemical and technological innovations, (3) chemical structure, and (4) biosynthetic pathway (Aniszewski 2015). There are some other classifications of alkaloids based on their natural sources and the similarity in the carbon skeleton. According to the position of the N-atom in the main structural element, alkaloids can be divided into five different groups: (1) Heterocyclic alkaloids, (2) Alkaloids with N-atoms in exocyclic position, including aliphatic amines, (3) Putrescence, spermidine and spermine alkaloids, (4) Peptide alkaloids and (5) Terpene and storied alkaloids (Hesse 2002).

Alkaloids are usually distributed non-homogeneously over plant tissues and the maximum alkaloid concentration in a plant can be made into any of its tissues, including leaves, fruits or seeds, root or bark. Different tissues of the same plants may possibly contain different alkaloids as well (Grinkevich and Safronich 1983, Hesse 2002). Some well-known alkaloids and their plant sources are listed in Table 2. Chemical structures of two alkaloids which can potentially be recovered from food production by-products, such as potato and tomato wastes, are represented in Fig. 2.

There is no common or recommended method for isolation of alkaloids due to their higher diversity. Alkaloids, which are slightly soluble in water, are soluble in ethanol, benzene, ether, and chloroform (Aniszewski 2015). Based on these characteristics, a number of extraction techniques for alkaloids are available, such as ultrasound-assisted extraction, pressurized liquid extraction, microwave assisted extraction, enzyme assisted extraction, Soxhlet extraction and solid–liquid extraction (Hossain et al. 2015).

Glycosides

Glycosides are organic compounds usually found in plants and may contain phenol, alcohol or sulphur compounds within their structure. They are characterized by a sugar portion or moiety attached by a special bond (mostly a glycosidic bond) to one or non-sugar functional compounds. Many plants store chemicals in the form of inactive glycosides, which can be activated by enzyme hydrolysis, causing the sugar part to be detached and making the chemical available for use (Brito-Arias 2007, Kabera et al. 2014). These plant glycosides are extremely diverse and mostly

Table 2. Some well-known alkaloids and their sources (Adapted from Kabera et al. 2014).

Alkaloid name	Source
Atropine	*Atropa belladonna, Darura stramonium, Mandragora officinarum*
Berberine	*Berberis* species, *Hydrastis, Canadensis, Xanthorhiza simplicissima, Phellodendron amurense, Coptis chinensis, Tinospora cordifolia, Argemone mexicana* and *Eschscholzia californica*
Codeine	*Papaver somniferum*
Coniine	*Conium macularum, Sarracenia flave*
Cytisine (baptitoxine, sophorine)	*Labum* and *Cytisus* of *Fabaceae* family, most extracted from seeds of *Cytisus laborinum*
Morphine	*Papaver somniferum* and poppy derivatives
Nicotine	Solanaceae plant family
Quinine	*Cinchona succirubra, C. calisya, C. ledgeriana*, plants of Rubiaceae family
Solanine	*Solanum tuberosum, S. lycopersiam, S. igrum*, plants of Solanaceae family
Strychnine	*Strychnos nux-vomica*, Loganiaceae plants family
Thebaine (paramorphine)	*Papaver bracteatum*
Tomatine	Green parts of tomato plants
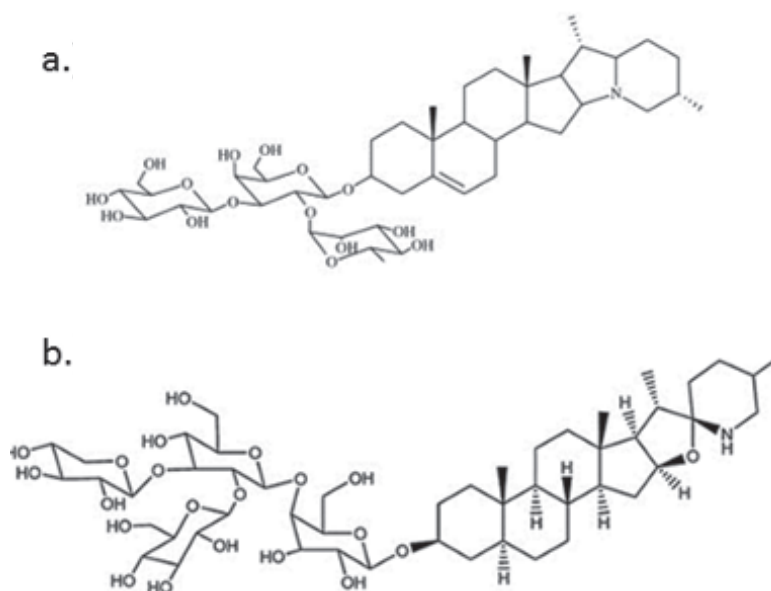
Figure 2. Chemical structures of; (a) solanine; and (b) α-tomatine (Adapted from Lee et al. 2013, Manrique-Moreno et al. 2014).

categorized as prodrugs since they remain inactive until they are hydrolyzed in the large intestine, leading to the release of the aglycone or the non-sugar portion, which is the right active constituent (Kabera et al. 2014). Glycosides are heterogeneous in structure and their classification is based on the nature of aglycone, which can be a wide range of molecular types, including phenols, quinines, terpenes and steroids (Kabera et al. 2014). Certain classifications are based on the therapeutic properties of glycosides, which can be further categorized into different groups, such as cardiac/steroidal, flavonoid, saponin, anthraquinone, cyanophore, isothiocyanate, alcohol, lactone, phenolic, coumarin, chromone and iridoid glycosides. Glycosides can also be categorized into four major groups based on the atoms involved in glycosidic linkage or the type of glycosidic bond: C-glycoside (when sugar moiety is lined with carbon atom), O-glycoside (with oxygen), S-glycoside (with sulphur) and N-glycoside (with nitrogen) (Brito-Arias 2007).

Glycosides contribute to the flavor, taste, color and quality of a number of plant-derived foods. For example, the most widespread anthocyanin which contributes color to fruits is cyanidin-3-glucoside (Fig. 3) (Kong et al. 2003, Shahidi and Ambigaipalan 2015). Additionally, therapeutic properties of glycosides include anticancer effects (Newman et al. 2008), expectorant, sedative, antidepressant, anticonvulsant activities and effect on the central nervous system (Fernández et al. 2006, Kabera et al. 2014, Wang et al. 2016). Glycosides can also be recovered from similar techniques used in isolation of alkaloids with water, methanol or ethanol used as the solvent for extraction (Brito-Arias 2007).

Phenolic compounds

Phenolic compounds are the most ubiquitous, diverse and widely distributed secondary plant metabolites lacking presence in bacteria, fungi and algae. To date, there are over
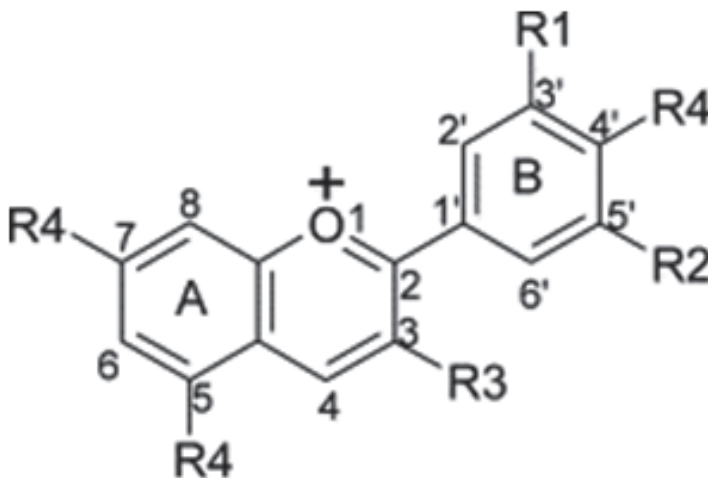
Figure 3. The flavylium cation. R1 and R2 are H, OH, or OCH3; R3 is a glycosyl or H; and R4 is OH or a glycosyl (Adapted from Kong et al. 2003).

8,000 different types of compounds and more than 4,000 flavonoids that have been classified (Tsao 2010). The *phenol*, as a broad term, refers to the chemical structure that defines the phenyl ring bearing one or more of the hydroxyl substituents. Therefore, the commonly used terminology referred to as polyphenols only further extends the structural component of the substance where multiple (at least two) phenol rings are present and contain at least one (or more) of the hydroxyl groups. This classification of phenolic compounds in literature is loosely used and is not necessarily related to the hydroxyl groups but also includes their functional derivatives (such as glycosides). Glycosides, discussed earlier in this chapter, actually contain the majority of plant polyphenols with different sugar units and acylated sugars at different positions of the polyphenolic skeleton. Interestingly, the term polyphenol could also include compounds, such as gossypol and oestrogene (Lattanzio 2013). Therefore, the classification of polyphenols in this chapter will be fundamentally based on different groups as a function of the number of phenol rings and on the structural elements that bind these rings together. Therefore, distinctions can be made from the flavonoids, phenolic acids, stilbenes and lignans (Manach et al. 2004, Tsao 2010, Naumovski 2015).

Flavonoids: Flavonoids are most predominant polyphenols and secondary metabolites with over 4,500 different compounds identified to date. In their structure, the most common feature that flavonoids share is the 2 aromatic rings (A and B) bound together by 3 carbon atoms, effectively forming an oxygenated heterocycle ring (C) (Fig. 4). The diversity of the type of heterocyclic rings is the primary driver of the functional classification of the flavonoids subgroups. Therefore, based on the functional properties, the flavonoids can be divided into flavonols, flavones, isoflavones, flavanones, anthocyanidins and flavanols (Manach et al. 2004, Huber and Rupasinghe 2009, Bernhoft 2010, Naumovski 2015).

Flavones: Flavones (Fig. 4b), are most commonly found in the skins of fruits and vegetables as well as in some culinary herbs. Two of the most common flavones in the edible plants are apigenin and luteolin. The apigenin is present in abundance in food sources, such as celery, onion (0.05 mg/100 g) and also in the culinary herbs, such as fresh sage and dried marjoram (4.4 mg/100 g). On the other hand, the luteolin is predominately present in fruit and vegetables, such as celery, broccoli, carrots, cabbages and apple skins at levels up to 60 mg/100 g (Neveu et al. 2010, Naumovski 2015).

Flavonols: Flavonols (Fig. 4c), are regarded as the most ubiquitous flavonoids present in foods and predominantly found as diverse glycosides with sugar moiety bound to the C-3 position. These compounds are found in different fruits and vegetables, such as onions, apples, grapes and some food products, such as ciders, wine and tea (Manach et al. 2004, Naumovski 2015). The main compounds—quercetin, myricetin and kaempferol—are the lead structures representing this group and although they are the most distributed compounds, their concentration levels in food are relatively low. For a majority of food sources, flavonol levels are less than 30 mg/kg of fresh weight for individual compounds (Manach et al. 2004). However, some food sources do contain relatively high levels of these compounds, such as cranberries, onions (with quercetin levels above 15 mg/100 g) and kale (with myricetin levels above 25 mg/100 g) (Bhagwat et al. 2013, Naumovski 2015). Interestingly, myricetin levels are
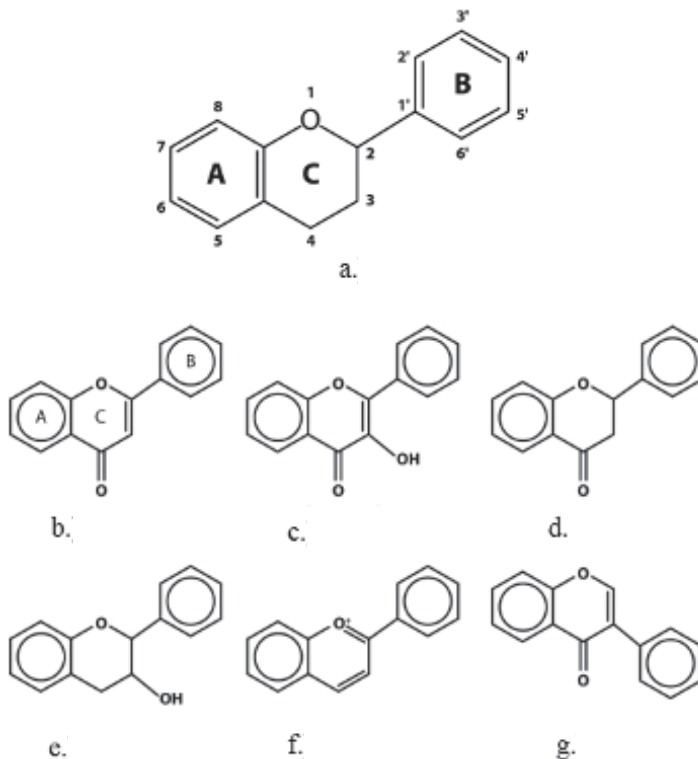
Figure 4. Common structure of flavonoids: a) containing 2 aromatic rings (A and B) and oxygenated heterocyclic ring (C); b) flavone; c) flavonol; d) flavanone; e) flavanol; f) anthocyanidin; and g) isoflavone.

related to the ripening stages of berries, with increased levels detected at fruit ripening (Ong and Khoo 1997).

Flavanones: Flavanones (Fig. 4d) are polyphenolic compounds that are rather unique for their presence in foods, as these compounds are predominately found in citrus fruits (Manach et al. 2003). From the food production perspective, orange juice is one of the most commonly represented foods that contains very high levels (90 per cent) of hesperidin (hesperidin-7-rutinoside) and much smaller percentage (10 per cent) being assigned to narirutin (naringenin-7-rutinoside) (Coelho et al. 2013, Naumovski 2015).

The food sources of flavanols (Fig. 4e) were reported to be in many fruits and vegetables, tea and a variety of different legumes, herbs and spices. Although these compounds exist in both monomer (catechins) and polymer forms (proanthocyanidins), catechins as flavanols have aroused significant interest in the latest literature due to their potential beneficial health effects (Mellor et al. 2010, Sathyapalan et al. 2010, Mellor et al. 2013, Lau et al. 2016). Catechins are found in fruits like apricots (250 mg/kg) but also present in food products, such as red wine (300 mg/L) (Manach et al.

2004, Naumovski 2015). However, green tea (Coelho et al. 2013) and chocolate (Gu et al. 2006) are two of the most catechin-dense foods available on the current market. Green tea in particular contains much higher levels of total catechin content while black tea has significantly lesser amounts due to the fermentation processes associated with black tea production (Vuong et al. 2010, Vuong et al. 2011). Proanthocyanidins are also referred to as tanins which are responsible for the astringent characteristics of fruits like apples, grapes and pears but also for the perceived bitterness of chocolate. Interestingly, these characteristics of foods diminish as the fruit ripens (Manach et al. 2004, Naumovski 2015).

Anthocyanidins: Anthocyanidins (Fig. 4f) are compounds commonly associated with the presence of different and vibrant colours (mainly blue and red) in numerous fruits, vegetables and flowers. These compounds are often bound to sugar groups and structurally, anthocyanidins are glycosylated polyhydroxy and polymethoxy derivatives of the flavium salts (Wallace 2011, Naumovski 2015). Despite the relatively large number of anthocyanidins already identified (over 630), only six (cyaniding, delphinidin, malvidin, pelargonidin, peonidin and pertuindin) form over 90 per cent of the anthocyanidins found in food products. The highest levels of anthocyanidins are reported in black grapes (up to 39.23 mg/100 g) and black currants (86.68 mg/100 g) (Neveu et al. 2010, Naumovski 2015).

Isoflavones: Isoflavones (Fig. 4g) are diphenolic compounds present in legumes, such as soybean and common black beans. These compounds have a structure very similar to mammalian estrogen and their consumption was reported to induce estrogenic and non-estrogenic effects. Two of the most predominant isoflavanones are genistein and daidzein with levels reaching 3 mg/g in various types of soybeans (Manach et al. 2004, Neveu et al. 2010, Naumovski 2015). Additionally, these compounds can also be found in different forms of conjugations, such as isoflavone glucosides (sugar conjugated) and acetyl- and malonyl glucosides.

Phenolic acids: Phenolic acids can be divided into two main categories, derivatives of benzoic acid and derivatives of cinnamic acid (Fig. 5) and these compounds are found free and as conjugates in several different foods. The cinammic acid derivatives commonly occur in foods than benzoic acid derivatives and predominately consist of coumaric (Fig. 5b1), caffeic (Fig. 5b2) and ferullic acids (Fig. 5b3). In Nature, phenolic acids are most commonly found in bound glycosylated derivatives of esters of quinic, shikimic and tartaric acids, except in the processed foods that has undergone freezing, sterilization or fermentation (Manach et al. 2004, Naumovski 2015).

Caffeic acid is the most abundant phenolic acid with over 75 per cent acid content of most fruits with highest concentrations seen in the outside layer of the fruit. The concentration to decreased during fruit ripening, but the overall quantities are proportional to the increase in fruit's size.

Ferullic acid, however, is predominantly found in seeds and cereal grains and may be responsible for up to 90 per cent of total polyphenolic content. Similarly to caffeic acid, the frullic acid is chiefly found in the outermost layer of wheat endosperm (aleurone and pericarp layers) and potential losses of this phenolic acid during flour production can be quite significant (Manach et al. 2004, Naumovski 2015).
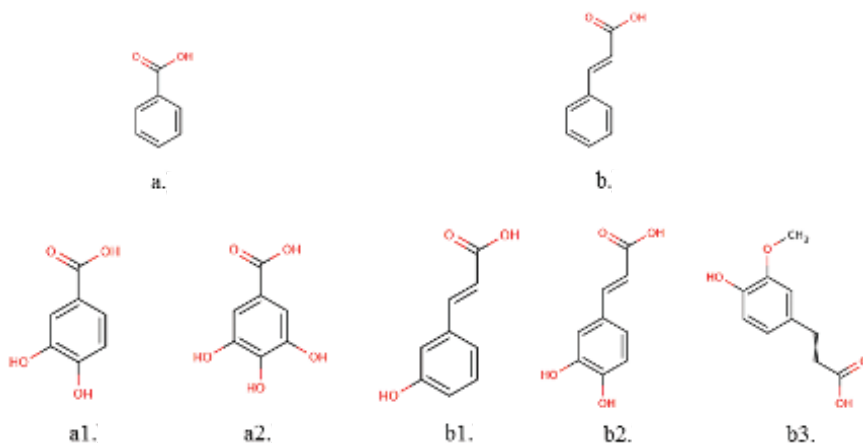
Figure 5. Structures of two classes of phenolic acids: a) bezoic acid; and b) Cinnamic acid and their derivatives; Protocafechuric acid–a1; Gallic acid–a2; Coumeric acid–b1; Caffeic acid–b2; and Ferullic acid–b3 (Adapted from Kim et al. 2016).

The benzoic acid content of fruit and vegetables is generally low, except in foods such as onions and some red fruits with values reported to be a few tens of mg/kg. Interestingly, tea is reported to have the most important source of gallic acid with concentrations reaching 4.5 g/kg (Neveu et al. 2010, Naumovski 2015, Naumovski et al. 2015).

Stilbenes: Stilbenes are one of the only polyphenols that are found in very small concentrations in the human diet due to very small quantities occurring naturally in foods (Neveu et al. 2010, Naumovski 2015). In this class of polyphenols, resveratrol (Fig. 6) is the most abundant stilbene found in a small number of edible plants. Resveratrol (trans-3,4',5-trihydroxystilbene) is a polyphenol commonly found in grapes and has been associated with several beneficial health effects chiefly driven via the anti-inflammatory metabolic regulation in humans (Christenson et al. 2016). Resveratrol is found in strawberries (0.35 mg/100 g) and red currants (1.57 mg/ 100 g) (Ehala et al. 2005). However, the most investigated and *advertised* food product of resveratrol occurrence is wine. It is found in the skin and seeds of grapes, but larger quantities are found in red wine (0.19 mg/100 ml). It is important to note that resveratrol is found in white and rose wines as well, but to a much smaller extent (around tenfold less). Furthermore, the quantity of resveratrol found in different varieties of red wine is mainly dependent on the grape variety and is also regulated by different external factors, such as geographical region and climatic factors that grapes are exposed to (Gambuti et al. 2007, Neveu et al. 2010, Naumovski 2015).

Lignans: The basic lignan structure is composed of two cinnamic acid residues (or their biogenetic equivalents) (Ayers and Lokie 1990) and as such, belong to a class of a very large group of pharmacologically active compounds (Teponno et al. 2016). Most of the lignans commonly occur freely in a variety of the human food sources. However a relatively small proportion also occurs as glycosides in wood and resin
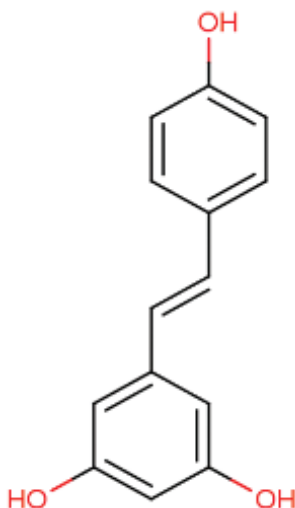
Figure 6. Chemical structure of resveratrol (*trans*-3,4',5-trihydroxystilbene) (Adapted from Kim et al. 2016).

of some plants. These compounds are also referred to as dimers possessing a fairly complex chemical structure. Further, a relatively few trimers and tetramers are also of relatively low molecular weight found in nearly all morphological structures of the plant itself. According to their structure, ligans can be classified into five main categories, namely, lignans, neolignans, norlignans, hybrid lignans and oligomeric lignans, which are further classified into their own respective subgroups (Landete 2012, Zhang et al. 2014, Teponno et al. 2016).

These fiber-related polyphenols are very common in foods with significant amounts of fiber, such as whole-grain products (Landete 2012). Additionally, lignans are also found in other food sources, such as nuts and oilseeds, cereals and breads as well some fruits with varying levels of concentrations (Manach et al. 2004, Landete 2012). A food source with the highest amount of lignans is flaxseed (around 300 mg/100 g) followed by sesame seeds (up to 30 mg/100 g), sunflower seeds (0.89 mg/100 g) and cashew nuts (0.63 mg/kg). Cereals also present a significant source of lignans with highest amounts being detected in rye (8.6 mg/100 g), wheat (3.2 mg/100 g) and oat (2.3 mg/100 g). Vegetables have high levels of lignans (0.19–2.3 mg/100 g) in sources such as cabbage, Brussel sprouts and kale, while the range of lignans in fruits is reported to range from 0 (banana) to 0.45 mg/100 g for apricot (Landete 2012).

Terpenoids

Bioactive plant constituents have been actively studied for their health-enhancing properties since numerous years and as described above, key bioactive plant-derived constituents include flavonoids, phenolic acids, carotenoids, tocopherols, alkaloids, lignans, tannins, salicylates, glucosinolates and triterpenoids (Han and Bakovic 2015).

Triterpenoids are Nature-derived compounds present in free form as well as in the form of numerous glycosides. The complex structures of triterpenoids mainly involve squalene derivatives, lanostanes, cycloartanes, dammaranes, euphanes, tirucallanes, tetranortriterpenoids, quassinoids, lupanes, oleananes, friedelanes, ursanes, hopanes, serratanes and other less known groups (Lesellier et al. 2012, Han and Bakovic 2015). The special triterpenic skeletons allow performance of chemical modifications in order to obtain many new derivatives with improved pharmacological activity (Lesellier et al. 2012). All forms of triterpenoids are widely distributed in edible and medicinal plants. Consequently they form an integral part of the human diet (Han and Bakovic 2015).

The three key triterpene groups include oleane, ursane and lupane triterpenes (Hill and Connolly 2011). The main triterpenoids found in the oleane category include oleanolic acid, erythrodiol and β-amyrin, whereas ursane and lupane families contain ursolic acid, uvaol; and lupeol, betulin and betulinic acid respectively (Han and Bakovic 2015). Oleanolic acid, maslinic acid, and β-amyrin are the chief compounds present in the oleanane triterpene family. These compounds are predominantly found in the skin of grapes, olives and tomatoes. Ursolic acid and uvaol are the chief compounds present in the ursane family. They are mainly present in the cuticle of apples (Han and Bakovic 2015). The chief compounds of lupine family, namely lupeol, betulin and betulinic acid are mainly found in the cuticle of mangoes and grape berries. Triterpenoids, in their free and esterified form are found to have low polarity. Therefore they are found in abundance in plant parts, such as surface cuticle waxes and stem bark (Szakiel et al. 2012). Therefore, fruit peels serve as a promising and highly available source material for such bioactive components (Jager et al. 2009).

Compared with plant vegetative organs, especially leaves, far less information is available regarding the triterpenoid content of fruit cuticular waxes (Szakiel et al. 2012). Fruit peels are a waste product of juice and canned products. Their utilisation to generate a value-added, therapeutically active, food ingredient can be economically beneficial (Wolfe and Liu 2003, Djilas et al. 2009). Triterpenoids, both in their natural form and as templates for synthetic modification, are of considerable interest to academia and industry. As previously indicated, food industries produce large volumes of wastes and the disposal of it may cause significant environmental pollution and burden. Millions of tonnes of apple, grape berry, olive, tomato, orange and other fruit peels are generated each year as agro-industrial waste. This could be utilized to formulate various useful pharmaceutical and/or nutraceutical applications (Mintz-Oron et al. 2008, Szakiel et al. 2012).

Bioactives from Agricultural and Food Production Wastes

Although the total alkaloid content in plants is usually low, the plant-based agricultural by-products in particular food production waste can be considered as a potential source for alkaloids. Various alkaloids have been successfully isolated from agricultural and food wastes, such as potato peels (Hossain et al. 2015), potato tubers (Petersson et al. 2013), green tea leaves (Bermejo et al. 2015), tomato roots (Nagaoka et al. 1993), tomato (fruit) (Yahara et al. 2004), citrus and orange peel (epicarp and mesocarp) (He et al. 2011), dried pepper fruits (*Capsicum frutescens*) (Santos et al. 2016), lupin grains (Przybylak et al. 2005, Sujak et al. 2006), barley (*Hordeum vulgare*),

rye (*Secale cereal*) (Aniszewski 2015), common wheat (*Triticum aestivum*), Triticale (Scott and Lawrence Guillaume 1982), Maté (*Ilex paraguariensis*) leaf (Clifford and Ramirez-Martinez 1990), cocoa beans (*Theobroma cacao*) (Nazaruddin et al. 2006), castor leaves (*Ricinus communis*) (Kang et al. 1985), coffee beans (Mehari et al. 2016) and Kolanut (*Cola nitida*) (Muhammad and Fatima 2014).

When plants are under stress due to improper storage conditions, mechanical damages, insect or pest attack, the injured plant tissues instigate synthesis of higher concentrations of alkaloids and other compounds (Chowański et al. 2016). For example, potatoes that have been exposed to light in the open or during storage may become green due to accumulation of chlorophyll, which may affect the surface (peel) or may penetrate into the flesh. Such tubers and damaged potato tubers usually possess higher levels of alkaloids. Therefore, isolation of alkaloid compounds from agricultural and food production waste is a feasible approach for economic development (Petersson et al. 2013, Chowański et al. 2016).

Since most common phenolic acids and flavonoids in plants are present in conjugated forms as esters or glycosides (Lu et al. 2011), agricultural and plant-based food wastes are among the best sources for recovering glycosides and its derivatives. Apple pomace, one of the major global waste products generated primarily during apple juice production, is rich in a vast array of polyphenolic compounds, including quercetin and phloretin glycosides with notable functional properties. For example, quercetin glycosides isolated from apple pomace showed excellent antioxidant properties compared to other phenolic compounds (Lu and Foo 2000). Apple peel skins (Lommen et al. 2000, Huber and Rupasinghe 2009) and seeds (Lu and Foo 1998) are rich in glycosides. Grape pomace as a by-product is approximately 20 per cent of the harvested grapes. Flavonol glycoside is one of the principal phenolic constituents of grape (*Vitis vinifera* cultivars) pomace (Schieber et al. 2001) and has been isolated from both grape fruit skins and seeds (Williams et al. 1983, Ruberto et al. 2007). Grape stem, the other major waste product in the wine industry, also possesses glycosides (Souquet et al. 2000, Spatafora et al. 2013). Glycosides have been identified and characterized from numerous fruits and fruit-based by-products, such as mango peel and puree (Schiebe et al. 2000, Schieber et al. 2001), kiwifruit pulp (Dawes and Keene 1999), bitter apricot seeds (*Prunus armeniaca* L., Rosaceae) (Tunçel et al. 1995), citrus fruits including lime, lemon, orange, grapefruit and tangerine peel (Mouly et al. 1994, Kanaze et al. 2004, Lu et al. 2011, Shahidi and Ambigaipalan 2015), black currant seeds (Lu and Yeap Foo 2003, Shahidi and Ambigaipalan 2015) and skins and seeds of blueberries and blueberry processing waste (Lee and Wrolstad 2004).

Vegetable-based food commodities, such as onion (*Allium cepa* L., Alliaceae) waste, which includes brown skin, the outer two fleshy leaves and the top and bottom bulbs (Schieber et al. 2001, Turner et al. 2006), potato peel (Reyes et al. 2005), lettuce and collard leaves (Young et al. 2005), cabbage (*Brassica*) leaves (Nielsen et al. 1993), pumpkin varieties, such as *Curcubita pepo* (Iheanacho and Udebuani 2009) and pericarp of red pepper fruit (*Capsicum annuum* L.) (Materska and Perucka 2005) have also been used in recovering glycosides. Various other agricultural and food production wastes including cottonseed as a by-product (Piccinelli et al. 2007), defatted soybean (Nemitz et al. 2015), tea leaves (Wan et al. 2009), almond hulls (*Prunus amygdalus*) (Sang et al. 2002), industrial horse chestnut (*Aesculus hippocastanum*) waste (Kapusta et al. 2007), green barley (*Hordeum vulgare* L.) leaves (Kitta et al. 1992) and seed

coat of lentils (Dueñas et al. 2002) and beans (Madhujith et al. 2004, Shahidi and Ambigaipalan 2015) are recognized as natural sources of glucosides.

Vegetative parts of certain culinary herbs and spices, such as ginger (*Zingiber officinale* Rosc.), thyme (*Thymus vulgaris* L.), parsley (*Petroselinum crispum* Mill.), curry leaves (*Murraya koenigii* L. Spreng), peppermint (*Mentha piperita* L.), turmeric (*Curcuma longa* L.), green onion scallion (*Allium fistulosum* L.), coriander (*Coriandrum sativum* L.) and Chinese star anise (*Illicium verum* Hook) also contain cardiac glycosides (Wang et al. 2011, Ramkissoon et al. 2016). Hence, portions of these herbs and spices which are unsuitable for culinary purposes can be potential sources of extracting glycosides.

Individual Sources and Potential Uses of Some of the Bioactives from Agricultural Food Waste

Apples and apple peel

Regular consumption of apples has been associated with prevention of chronic diseases, such as lung cancer, cardiovascular disease, symptoms of chronic obstructive pulmonary disease and the risk of thrombotic stroke (He and Liu 2007, Szakiel et al. 2012). Apple peel is found to contain greater antioxidant and antiproliferative activity than the flesh (Wolfe and Liu 2003), thus suggesting that the peel contains a major share of the bioactive phytochemicals (Cefarelli et al. 2006). The triterpenoid composition of apple peel and its noted pharmacological properties are summarised in Tables 3 and 4. Previous reports suggest that the method of cultivation and post-harvest conditions, including cold storage of fruit, can influence the triterpenoid composition of the cuticular wax (Szakiel et al. 2012).

Grape berry

Grapevine (*Vitis vinifera* L.) consumption is associated with reduction of chronic illnesses, such as cancer, cardiovascular diseases, ischemic stroke, neurodegenerative disorders and aging (Yadav et al. 2009, Ali et al. 2010). Grapevine-derived products (fresh berries, raisins, juice, wine) are well known for their antioxidant content and therefore, grape extracts are widely incorporated in various cosmetic formulas. Bioactive components, including polyphenols, resveratrol, hydroxytyrosol and melatonin, may provide health benefits associated with regular consumption of grape products (Leifert and Abeywardena 2008, Ali et al. 2010). The triterpenoid composition of grape berry skin and its noted pharmacological properties are summarised in Tables 5 and 6. In addition to oleanolic acid, other triterpenoids have been identified in grape berry skin, including oleanolic aldehyde, erythrodiol and a group of phytosterols and their derivatives (e.g., β-sitosterol, campesterol, stigmasterol, and lanosterol) (Dagna et al. 1982, Orban et al. 2009, Zhang et al. 2014).

Olives

The olive (*Olea europaea* L.) is a fruit of substantial agricultural importance in the Mediterranean region. Olive tree cultivation started approximately 6,000 years ago

Table 3. Summary of the triterpenoid composition of apple peel (Adapted from Szakiel et al. 2012).

Fruit	Composition	Amount	Main compounds	Reference
Apple (*Malus pumila* Mill.)	Euscaphic acid; 2a,3a-dihydroxy-olean-12-en-28-oic acid; 2a,3a-dihydroxy-urs-12-en-28-oic acid; 2a-hydroxyursolic acid; ursolic acid, uvaol	77% of the peel extract	Ursolic acid (98% of triterpenoid mixture)	(Ma et al. 2005)
Apple (*Malus domestica* Borkh.) cv. Holsteiner Cox	Oleanolic acid; ursolic acid; uvaol	0.34–0.42% of the peel extract	Ursolic acid (0.28–0.34% of the peel extract)	(Ellgardt 2006)
Apple (*M. pumila* Mill.) cv. Red Delicious	3b-cis-p-coumaroyloxy-2a-hydroxyolean-12-en-28-oic acid; 3b-cis-p-coumaroyloxy-2a- hydroxyurs-12-en-28-oic acid; 3b,28-dihydroxy-12-ursene; 3b,13b-dihydroxyurs-11-en-28-oic acid; 2a-hydroxyursolic acid; maslinic acid; 3b-trans-cinnamoyloxy-2a-hydroxyurs-12-en-28-oic acid; 3b-trans-p-cinnamoyloxy-2a-hydroxyolean-12-en-28-oic acid; 3b-trans-p-coumaroyloxy-2a-hydroxyolean-12-en-28-oic acid; 3b-trans-p-coumaroyloxy-2a-hydroxyurs-12-en-28-oic acid; 2a,3b,13b-trihydroxyurs-11-en-28-oic acid; ursolic acid	0.15–19.5% of the peel extract	Ursolic acid (0.15% of the mass of fresh peels, 18% of the peel extract)	(He and Liu 2007)

Table 4. Summary of the pharmacological properties of triterpenoids found in apple peel seen in *in vitro* models (Adapted from Szakiel et al. 2012).

Pharmacological properties	Reference
Antitumor activity, with inhibitory activity against four tumour cell lines, HL-60, BGC, Bel-7402, and HeLa, with ED50 values ranging from 45 to 72 µg/ml	(Ma et al. 2005)
Antiproliferative activities against human cell lines of HepG2 liver cancer, MCF-7 breast cancer and Caco-2 colon cancer	(Yamaguchi et al. 2008)
Antitumorigenic effects—suppression of p65 phosphorylation, TNF-induced expression of cyclin D1, cyclooxygenase 2 (COX-2) and matrix metalloproteinase 9, which are involved in the initiation, promotion and metastasis of tumours	(He and Liu 2007)

Table 5. A summary of the triterpenoid and phytosterol composition of grape berry skin (Adapted from Szakiel et al. 2012).

Fruit	Composition	Amount	Main compounds	Reference
Grape berry (*Vitis vinifera* L.) cv. Cabernet Sauvignon	Oleanolic acid; oleanolic aldehyde; β-sitosterol; β-sitosterol 3-O-β–D-glucoside; β-sitosterol-60-linolenoyl-3-O-β-D-glucopyranoside	0.075% of fresh skin mass	Oleanolic acid (86% of triterpenoid mixture)	(Zhang et al. 2004)
Grape berry (*V. vinifera* L.)	Oleanolic acid; β-sitosterol; β-sitosterol-3-O-β–D-glucoside	0.027% of fresh berry mass	Oleanolic acid (0.003–0.016% of fresh berry mass)	(Orban et al. 2009)

Table 6. Summary of the reported pharmacological properties of triterpenoids found in grape berry skin (Adapted from Szakiel et al. 2012).

Pharmacological properties	Reference
Anticancer, anti-inflammatory, antidiabetogenic, antimicrobial, hepato- and cardioprotective, anti-HIV and anti-multiple sclerosis effects	(Liu 2005, Martin et al. 2010)
Regulation of insulin secretion, activity against type-2 diabetes and inflammation	(Zhang et al. 2004)
Hepato-protective activity, prevention and treatment of liver disorders, to treat diarrhoea, hepatitis and stomach aches	(Liu et al. 2010)
Antimicrobial activity against Streptococcus mutans and Porphyromonas gingivalis, potential benefits to oral health and disease prevention	(Wu 2009)
Serum cholesterol lowering, cancer preventive, antimutagenic and anti-inflammatory activities	(Awad and Fink 2000, Piironen et al. 2000, Villasenor et al. 2002)
Antiprotozoal and chemo preventive activities	(Gallo and Sarachine 2009)

and thus the olive is the oldest cultivated tree (Szakiel et al. 2012). Olive oil is one of the key components in the traditional Mediterranean diet and has significant nutritional and medicinal properties. These include reduction of the risk of coronary heart disease and atherosclerosis, prevention of several types of cancer and modification of the immune and inflammatory responses (Ortega 2006). The potential of triterpenoids and some other polyphenols present in olive oil has not been explored to its full potential (Stiti and Hartmann 2012). The triterpenoid composition of olive oil and its pharmacological properties are summarized in Tables 7 and 8. The triterpenoids composition in olives that are sold in the market is influenced by cultivar or the stage of fruit ripeness, and also the method of processing (Romero et al. 2010).

Tomato

Tomatoes (*Solanum lycopersicum* L. or *Lycopersicon esculentum* L.) are one of the most important fruit crops globally. They are cultivated practically in every country in the world in outdoor fields, glass houses and net houses (Szakiel et al. 2012) with the triterpenoid composition summarised in Table 9. The triterpenoid levels in the fruit vary considerably during various stages of fruit development. For example, the levels of the most abundant triterpenols (α-, β- and δ-amyrins) increase significantly 25–42 days after flower anthesis (Mintz-Oron et al. 2008). The potential pharmacological properties of bioactives identified from tomato skin include prevention of certain types of cancer, liver disorders, heart disease, osteoporosis, cataracts, anti-allergic, antidepressant, anti-inflammatory, anti-nociceptive, antipruritic, anxiolytic, gastro protective and hepato-protective activities (Soldi et al. 2008, Melo et al. 2010, Ching et al. 2011).

Table 7. Summary of the triterpenoid composition of olive skin (Adapted from Szakiel et al. 2012).

Fruit	Composition	Amount	Main compounds	Reference
Olive (*Olea europaea* L.) cv. Coratina	α-amyrin; β-amyrin; betulinic acid; erythrodiol; maslinic acid; oleanolic acid; β-sitosterol, stigmasterol, uvaol	0.075% of fresh skin mass	Oleanolic acid (86% of triterpenoid mixture)	(Bianchi et al. 1992)
Olive (*O. europaea* L.) cv. Arbequina	Maslinic acid; oleanolic acid	0.23 and 0.19% of Fruit, in green and black fruit, respectively	Oleanolic acid (0.003–0.016% of fresh berry mass)	(Guinda et al. 2010)

Table 8. Summary of the pharmacological properties of triterpenoids found in olive skin (Adapted from Szakiel et al. 2012).

Pharmacological properties	Reference
Anticancer, antihyperglycemic, and antiparasitic activities	(De Pablos et al. 2010, Moneriz et al. 2011)
Antiproliferative effect on HT-29 cells (EC50 of 160 μmol/l)	(Juan et al. 2008)
Prevention and treatment of hyperlipidemia	(Liu et al. 2011)
Prevention and treatment of brain cancers, potent inhibitory activity against human 1321N1 astrocytoma cells	(Wu 2009)
Antiparasitic properties with activity against *Plasmodium falciparum*, *Eimeria tenella*, and *Toxoplasma gondii*	(De Pablos et al. 2010, Moneriz et al. 2011)

Table 9. Summary of the triterpenoid composition of tomato skin (Adapted from Szakiel et al. 2012).

Fruit	Composition	Amount	Main compounds	Reference
Tomato (*L. Esculentum* L.)	α-amyrin; β-amyrin; δ-amyrin; bauerenol; cycloartenol; germanicol; lupeol; multiflorenol; β-sitosterol; stigmasterol; taraxasterol; ω-taraxasterol; taraxerol	13.7% of the total wax extract (average from 26 cultivars)	δ-amyrin (5.6% of wax extract, i.e., 41.2% of total triterpenoids); β-amyrin (3.2% of wax extract); α-amyrin (3% of wax extract)	(Bauer et al. 2004)
Tomato (*L. esculentum* L.) cv. MicroTom (wild-type)	α-amyrin; β-amyrin; β-amyrin derivative; δ-amyrin; sterol; lanosterol; lupeol derivative I; multiflorenol; β-sitosterol; stigmasterol; taraxasterol; ω-taraxasterol; taraxerol	21% of the total wax extract (in mature fruit)	α-, β-, δ-amyrins (76–91% of total triterpenoids)	(Leide et al. 2007)

Conclusion

Bioactive compounds have aroused significant interest in the recent past, predominately due to their antioxidant properties, which suppress and inhibit the production of common free radicals, such as superoxide anion and hydroxyl radical. Although these properties are well described in several *in vitro* studies, human and animal data still remain controversial (Lau et al. 2016, Mellor and Naumovski 2016). From the perspective of human consumption, it is important to note that though these compounds may be present in very high doses in some food products, their intake and absorption is regulated by the food intake and combination of different foods independently, whether they are consumed as a pure compound (Naumovski et al. 2015) or as a part of the polyphenolic matrix (Chow et al. 2005, Stalmach et al. 2008). However, formulations based on nanotechnology are proposed to replace the conventional dosage forms to address this concern (Chen et al. 2011). Much of the data supporting the concept of beneficial effects of these compounds is based on *in vitro* and animal model studies, with conflicting data often coming from clinical trials in humans. In some cases, such as with resveratrol, the dietary consumption of the compound is well below the threshold required to produce any significant physiological effect. Therefore, extraction, isolation and purification of individual compounds from the food matrix has already aroused significant levels of interest in the food and pharmaceutical industry. This search for pure compounds has also created a requirement for the production of foods that are primary carriers of bioactives where

the utilisation of agricultural food waste can be seen as a perfect fit to this part of the food industry. The main reason for this is due to the fact that agricultural food waste can contain significant levels of individual bioactives and rather than waste being re-used in the form of a landfill, it can be directed to re-utilisation of bioactives. Nevertheless, the presence of bioactives in foods is of crucial importance, not only from the perspective of potential beneficial health effects in humans, but also from the protective role that these compounds play in the overall plant metabolism.

References

Ali, K., F. Maltese, Y. H. Choi and R. Verpoorte. 2010. Metabolic constituents of grapevine and grape-derived products. Phytochem. Rev. 9(3): 357–378.

Aniszewski, T. 2015. Definition, typology, and occurrence of alkaloids. Alkaloids. Boston, Elsevier: 1–97.

Awad, A. B. and C. S. Fink. 2000. Phytosterols as anticancer dietary components: Evidence and mechanism of action. J. Nutr. 130(9): 2127–2130.

Ayers, D. C. and J. D. Lokie. 1990. Lignans: Chemical, Biological and Clinical Properties. Cambridge, United Kingdom, Cambridge University Press.

Baiano, A. 2014. Recovery of biomolecules from food wastes—a review. Molecules 19(9): 14821–14842.

Bauer, S., E. Schulte and H. P. Their. 2004. Composition of the surface wax from tomatoes—I. Identification of the components by GC/MS. European Food Research and Technology 219(3): 223–228.

Bermejo, D. V., J. A. Mendiola, E. Ibáñez, G. Reglero and T. Fornari. 2015. Pressurized liquid extraction of caffeine and catechins from green tea leaves using ethyl lactate, water and ethyl lactate + water mixtures. Food and Bioproducts Processing 96: 106–112.

Bernhoft, A. 2010. A brief review of bioactive compounds in plants. Bioactive Compounds in Plants—Benefits and Risks for Man and Animals. Oslo, Norway, Norw. Acad. Sc. and Lett.

Bhagwat, S., D. B. Haytowitz and J. M. Holden. 2013. Database for the Flavonoid Content of Selected Foods. Nutrient Data Laboratory, USDA Department of Agriculture.

Bianchi, G., C. Murelli and G. Vlahov. 1992. Surface waxes from olive fruits. Phytochemistry 31(10): 3503–3506.

Biesalski, H. K., L. O. Dragsted, I. Elmadfa, R. Grossklaus, M. Muller, D. Schrenk, P. Walter and P. Weber. 2009. Bioactive compounds: Definition and assessment of activity. Nutrition 25(11-12): 1202–1205.

Biesalski, H. K., L. O. Dragsted, I. Elmadfa, R. Grossklaus, M. Muller, D. Schrenk, P. Walter and P. Weber. 2009. Bioactive compounds: Safety and efficacy. Nutrition 25(11-12): 1206–1211.

Brito-Arias, M. 2007. Synthesis and Characterization of Glycosides. New York, USA, Springer Science+Business Media, LLC.

Cefarelli, G., B. D'Abrosca, A. Fiorentino, A. Izzo, C. Mastellone, S. Pacifico and V. Piscopo. 2006. Free-radical-scavenging and antioxidant activities of secondary metabolites from reddened cv. Annurca apple fruits. J. Agric. Food Chem. 54(3): 803–809.

Chen, M., Z. Zhong, W. Tan, S. Wang and Y. Wang. 2011. Recent advances in nanoparticle formulation of oleanolic acid. Chin. Med. 6(1): 20.

Ching, J., H. S. Lin, C. H. Tan and H. L. Koh. 2011. Quantification of alpha- and beta-amyrin in rat plasma by gas chromatography-mass spectrometry: Application to preclinical pharmacokinetic study. Journal of Mass Spectrometry 46(5): 457–464.

Chow, H. H., I. A. Hakim, D. R. Vining, J. A. Crowell, J. Ranger-Moore, W. M. Chew, C. A. Celaya, S. R. Rodney, Y. Hara and D. S. Alberts. 2005. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of Polyphenon E in healthy individuals. Clin. Cancer Res. 11(12): 4627–4633.

Chowański, S., Z. Adamski, P. Marciniak, G. Rosiński, E. Büyükgüzel, K. Büyükgüzel, P. Falabella, L. Scrano, E. Ventrella, F. Lelario and S. A. Bufo. 2016. A review of bioinsecticidal activity of Solanaceae alkaloids. Toxins 8(3): 60.

Christenson, J., S. J. Whitby, D. D. Mellor, J. Thomas, A. McKune, P. D. Roach and N. Naumovski. 2016. The effects of Resveratrol supplementation in overweight and obese humans—A systematic review of randomised trials. Metab. Syndr. Relat. Disord. In Press.

Clifford, M. N. and J. R. Ramirez-Martinez. 1990. Chlorogenic acids and purine alkaloids contents of Maté (*Ilex paraguariensis*) leaf and beverage. Food Chemistry 35(1): 13–21.

Coelho, R. C., H. H. Hermsdorff and J. Bressan. 2013. Anti-inflammatory properties of orange juice: Possible favorable molecular and metabolic effects. Plant Foods Hum. Nutr. 68(1): 1–10.

Covolo, L., M. Capelli, E. Ceretti, D. Feretti, L. Caimi and U. Gelatti. 2013. Nutritional supplements for diabetes sold on the internet: business or health promotion? BMC Public Health 13: 777.

Cragg, G. M. and D. J. Newman. 2005. Plants as a source of anti-cancer agents. J. Ethnopharmacol. 100(1-2): 72–79.

Cragg, G. M. and D. J. Newman. 2013. Natural products: A continuing source of novel drug leads. Biochim. Biophys. Acta 1830(6): 3670–3695.

Dagna, L., G. Gasparini, M. L. Icardi and E. Sesia. 1982. Study of some components of the unsaponifiable fraction in the skin of grapes. American Journal of Enology and Viticulture 33(4): 201–206.

Dawes, H. M. and J. B. Keene. 1999. Phenolic composition of kiwifruit juice. Journal of Agricultural and Food Chemistry 47(6): 2398–2403.

De Pablos, L. M., M. F. dos Santos, E. Montero, A. Garcia-Granados, A. Parra and A. Osuna. 2010. Anticoccidial activity of maslinic acid against infection with Eimeria tenella in chickens. Parasitol. Res. 107(3): 601–604.

Dembitsky, V. M. 2014. Naturally-occurring bioactive Cyclobutane-containing (CBC) alkaloids in fungi, fungal endophytes and plants. Phytomedicine 21(12): 1559–1581.

Djilas, S., J. Canadanovic-Brunet and G. Cetkovic. 2009. By-products of fruits processing as a source of phytochemicals. Chemical Industry & Chemical Engineering Quarterly 15(4): 191–202.

Dueñas, M., T. Hernández and I. Estrella. 2002. Phenolic composition of the cotyledon and the seed coat of lentils (*Lens culinaris* L.). European Food Research and Technology 215(6): 478–483.

Ehala, S., M. Vaher and M. Kaljurand. 2005. Characterization of phenolic profiles of Northern European berries by capillary electrophoresis and determination of their antioxidant activity. J. Agric. Food Chem. 53(16): 6484–6490.

Ellgardt, K. 2006. Triterpenes in Apple Cuticle of Organically and IP Cultivated Apples. Bachelor project in the Dannish-Swedish Horticulture Programme, Sveriges Lantbruksuniversitet.

Evans, D. A. and C. H. Mitch. 1982. Studies directed towards the total synthesis of morphine alkaloids. Tetrahedron Lett. 23(3): 285–288.

FAO. 2011. Global Food Losses and Waste. Extent, Causes and Prevention. Rome, Italy, Food and Agriculture Organization of the United Nations.

Fernández, S. P., C. Wasowski, L. M. Loscalzo, R. E. Granger, G. A. R. Johnston, A. C. Paladini and M. Marder. 2006. Central nervous system depressant action of flavonoid glycosides. Eur. J. Pharmacol. 539(3): 168–176.

Fugh-Berman, A. and A. Myers. 2004. Citrus aurantium, an ingredient of dietary supplements marketed for weight loss: Current status of clinical and basic research. Exp. Biol. and Med. 229(8): 698–704.

Gallo, M. B. C. and M. J. Sarachine. 2009. Biological activities of Lupeol. Int. J. Biomed. Pharm. Sci. 3(1): 46–66.

Gambuti, A., D. Strollo, A. Erbaggio, L. Lecce and L. Moio. 2007. Effect of winemaking practices on color indexes and selected bioactive phenolics of Aglianico wine. J. Food Sci. 72(9): S623–628.

Godfray, H. C., J. Pretty, S. M. Thomas, E. J. Warham and J. R. Beddington. 2011. Global food supply. Linking policy on climate and food. Science 331(6020): 1013–1014.

Grinkevich, N. I. and L. N. Safronich. 1983. Chemical Analysis of Medicinal Plants. Moscow, Vysshaya Shkola.

Gu, L., S. E. House, X. Wu, B. Ou and R. L. Prior. 2006. Procyanidin and catechin contents and antioxidant capacity of cocoa and chocolate products. J. Agric. Food Chem. 54(11): 4057–4061.

Guinda, A., M. Rada, T. Delgado, P. Gutierrez-Adanez and J. M. Castellano. 2010. Pentacyclic triterpenoids from olive fruit and leaf. J. Agric. Food Chem. 58(17): 9685–9691.

Han, N. and M. Bakovic. 2015. Biologically active triterpenoids and their cardioprotective and anti-inflammatory effects. J. Bioanal. Biomed. S12(005): 11.

He, D., Y. Shan, Y. Wu, G. Liu, B. Chen and S. Yao. 2011. Simultaneous determination of flavanones, hydroxycinnamic acids and alkaloids in citrus fruits by HPLC-DAD–ESI/MS. Food Chem. 127(2): 880–885.

He, X. and R. H. Liu. 2007. Triterpenoids isolated from apple peels have potent antiproliferative activity and may be partially responsible for apple's anticancer activity. J. Agric. Food Chem. 55(11): 4366–4370.

Hesse, M. 2002. Alkaloids: Nature's Curse or Blessing? Zurich, John Wiley & Sons.

Hill, R. A. and J. D. Connolly. 2011. Triterpenoids. Nat. Prod. Rep. 28(6): 1087–1117.

Hossain, M. B., I. Aguiló-Aguayo, J. G. Lyng, N. P. Brunton and D. K. Rai. 2015. Effect of pulsed electric field and pulsed light pre-treatment on the extraction of steroidal alkaloids from potato peels. Innov. Food Sc. Eme. Tech. 29: 9–14.

Huber, G. M. and H. P. V. Rupasinghe. 2009. Phenolic profiles and antioxidant properties of apple skin extracts. Journal of Food Science 74(9): C693–C700.

Iheanacho, K. M. and A. C. Udebuani. 2009. Nutritional composition of some leafy vegetables consumed in Imo state, Nigeria. Journal of Applied Sciences and Environmental Management 13: 3.

Jager, S., H. Trojan, T. Kopp, M. N. Laszczyk and A. Scheffler. 2009. Pentacyclic triterpene distribution in various plants—Rich sources for a new group of multi-potent plant extracts. Molecules 14(6): 2016–2031.

Juan, M. E., J. M. Planas, V. Ruiz-Gutierrez, H. Daniel and U. Wenzel. 2008. Antiproliferative and apoptosis-inducing effects of maslinic and oleanolic acids, two pentacyclic triterpenes from olives, on HT-29 colon cancer cells. Br. J. Nutr. 100(1): 36–43.

Kabera, J. N., E. Semana, A. R. Mussa and X. He. 2014. Plant secondary metabolites: Biosynthesis, classification, function and pharmacological properties. J. Pharm. Pharmacol. 2(377–392).

Kanaze, F. I., E. Kokkalou, M. Georgarakis and I. Niopas. 2004. Validated high-performance liquid chromatographic method utilizing solid-phase extraction for the simultaneous determination of naringenin and hesperetin in human plasma. Journal of Chromatography B 801(2): 363–367.

Kang, S. S., G. A. Cordell, D. D. Soejarto and H. H. S. Fong. 1985. Alkaloids and flavonoids from Ricinus communis. Journal of Natural Products 48(1): 155–156.

Kapusta, I., B. Janda, B. Szajwaj, A. Stochmal, S. Piacente, C. Pizza, F. Franceschi, C. Franz and W. Oleszek. 2007. Flavonoids in horse chestnut (*Aesculus hippocastanum*) seeds and powdered waste water byproducts. Journal of Agricultural and Food Chemistry 55(21): 8485–8490.

Kim, S., P. A. Thiessen, E. E. Bolton, J. Chen, G. Fu, A. Gindulyte, L. Han, J. He, S. He, B. A. Shoemaker, J. Wang, B. Yu, J. Zhang and S. H. Bryant. 2016. PubChem substance and compound databases. Nucleic Acids Res. 44(D1): D1202–1213.

Kitta, K., Y. Hagiwara and T. Shibamoto. 1992. Antioxidative activity of an isoflavonoid, 2-O-glycosylisovitexin isolated from green barley leaves. Journal of Agricultural and Food Chemistry 40(10): 1843–1845.

Kong, J. -M., L. -S. Chia, N. -K. Goh, T. -F. Chia and R. Brouillard. 2003. Analysis and biological activities of anthocyanins. Phytochemistry 64(5): 923–933.

Kumar, A., A. Singh and E. Ekavali. 2015. A review on Alzheimer's disease pathophysiology and its management: An update. Pharmacol. Rep. 67(2): 195–203.

Landete, J. M. 2012. Plant and mammalian lignans: A review of source, intake, metabolism, intestinal bacteria and health. Food Res. Int. 46(1): 410–424.

Lattanzio, V. 2013. Phenolic Compounds: Introduction. Natural Products. K. G. Ramawat and J. M. Merillon. Berlin, Springer-Verlag.

Lau, S. O., E. N. Georgousopoulou, J. Kellett, J. Thomas, A. McKune, D. D. Mellor, P. D. Roach and N. Naumovski. 2016. The effect of dietary supplementation of green tea catechins on cardiovascular disease risk markers in humans: A systematic review of clinical trials. Beverages 2(2): 16.

Lee, J. and R. E. Wrolstad. 2004. Extraction of anthocyanins and polyphenolics from blueberry processing waste. Journal of Food Science 69(7): 564–573.

Lee, S. -T., P. -F. Wong, J. D. Hooper and M. R. Mustafa. 2013. Alpha-tomatine synergises with paclitaxel to enhance apoptosis of androgen-independent human prostate cancer PC-3 cells *in vitro* and *in vivo*. Phytomedicine 20(14): 1297–1305.

Leide, J., U. Hildebrandt, K. Reussing, M. Riederer and G. Vogg. 2007. The developmental pattern of tomato fruit wax accumulation and its impact on cuticular transpiration barrier properties:

Effects of a deficiency in a beta-ketoacyl-coenzyme A synthase (LeCER6). Plant Physiol. 144(3): 1667–1679.

Leifert, W. R. and M. Y. Abeywardena. 2008. Cardioprotective actions of grape polyphenols. Nutr. Res. 28(11): 729–737.

Lesellier, E., E. Destandau, C. Grigoras, L. Fougere and C. Elfakir. 2012. Fast separation of triterpenoids by supercritical fluid chromatography/evaporative light scattering detector. J. Chromatogr. A 1268: 157–165.

Liu, J. 2005. Oleanolic acid and ursolic acid: Research perspectives. J. Ethnopharmacol. 100(1-2): 92–94.

Liu, J., H. Sun, J. Shang, Y. Yong and L. Zhang. 2011. Effect of olive pomace extracts on hyperlipidaemia. Nat. Prod. Res. 25(12): 1190–1194.

Liu, T., J. Zhao, H. Li and L. Ma. 2010. Evaluation on anti-hepatitis viral activity of *Vitis vinifer* L. Molecules 15(10): 7415–7422.

Lommen, A., M. Godejohann, D. P. Venema, P. C. H. Hollman and M. Spraul. 2000. Application of directly coupled HPLC−NMR−MS to the identification and confirmation of quercetin glycosides and phloretin glycosides in apple peel. Analytical Chemistry 72(8): 1793–1797.

Lu, L. and L. Y. Foo. 2000. Antioxidant and radical scavenging activities of polyphenols from apple pomace. Food Chemistry 68(1): 81–85.

Lu, M., B. Yuan, M. Zeng and J. Chen. 2011. Antioxidant capacity and major phenolic compounds of spices commonly consumed in China. Food Research International 44(2): 530–536.

Lu, Y. and L. Y. Foo. 1998. Constitution of some chemical components of apple seed. Food Chemistry 61(1-2): 29–33.

Lu, Y. and L. Yeap Foo. 2003. Polyphenolic constituents of blackcurrant seed residue. Food Chemistry 80(1): 71–76.

Ma, C. M., S. Q. Cai, J. R. Cui, R. Q. Wang, P. F. Tu, M. Hattori and M. Daneshtalab. 2005. The cytotoxic activity of ursolic acid derivatives. Eur. J. Med. Chem. 40(6): 582–589.

Madhujith, T., M. Naczk and F. Shahidi. 2004. Antioxidant activity of common beans (*Phaseolus vulgaris* L.). Journal of Food Lipids 11(3): 220–233.

Manach, C., C. Morand, A. Gil-Izquierdo, C. Bouteloup-Demange and C. Remesy. 2003. Bioavailability in humans of the flavanones hesperidin and narirutin after the ingestion of two doses of orange juice. Eur. J. Clin. Nutr. 57(2): 235–242.

Manach, C., A. Scalbert, C. Morand, C. Remesy and L. Jimenez. 2004. Polyphenols: Food sources and bioavailability. Am. J. Clin. Nutr. 79(5): 727–747.

Manrique-Moreno, M., J. Londoño-Londoño, M. Jemioła-Rzemińska, K. Strzałka, F. Villena, M. Avello and M. Suwalsky. 2014. Structural effects of the Solanum steroids solasodine, diosgenin and solanine on human erythrocytes and molecular models of eukaryotic membranes. BBA Biomembranes 1838(1, Part B): 266–277.

Martin, R., J. Carvalho-Tavares, M. Hernandez, M. Arnes, V. Ruiz-Gutierrez and M. L. Nieto. 2010. Beneficial actions of oleanolic acid in an experimental model of multiple sclerosis: A potential therapeutic role. Biochem. Pharmacol. 79(2): 198–208.

Materska, M. and I. Perucka. 2005. Antioxidant activity of the main phenolic compounds isolated from hot pepper fruit (*Capsicum annuum* L.). Journal of Agricultural and Food Chemistry 53(5): 1750–1756.

Mehari, B., M. Redi-Abshiro, B. S. Chandravanshi, M. Atlabachew, S. Combrinck and R. McCrindle. 2016. Simultaneous determination of alkaloids in green coffee beans from ethiopia: Chemometric evaluation of geographical origin. Food Analytical Methods 9(6): 1627–1637.

Mellor, D. D., T. Sathyapalan, E. S. Kilpatrick, S. Beckett and S. L. Atkin. 2010. High-cocoa polyphenol-rich chocolate improves HDL cholesterol in Type 2 diabetes patients. Diabet. Med. 27(11): 1318–1321.

Mellor, D. D., L. A. Madden, K. A. Smith, E. S. Kilpatrick and S. L. Atkin. 2013. High-polyphenol chocolate reduces endothelial dysfunction and oxidative stress during acute transient hyperglycaemia in Type 2 diabetes: A pilot randomized controlled trial. Diabet. Med. 30(4): 478–483.

Mellor, D. D. and N. Naumovski. 2016. Effect of cocoa in diabetes: The potential of the pancreas and liver as key target organs, more than an antioxidant effect? International Journal of Food Science and Technology 51(4): 829–841.

Melo, C. M., K. M. M. B. Carvalho, L. C. D. S. Neves, T. C. Morais, V. S. Rao, F. A. Santos, G. A. D. Brito and M. H. Chaves. 2010. Alpha, beta-amyrin, a natural triterpenoid ameliorates L-arginine-induced acute pancreatitis in rats. World Journal of Gastroenterology 16(34): 4272–4280.

Mintz-Oron, S., T. Mandel, I. Rogachev, L. Feldberg, O. Lotan, M. Yativ, Z. Wang, R. Jetter, I. Venger, A. Adato and A. Aharoni. 2008. Gene expression and metabolism in tomato fruit surface tissues. Plant Physiol. 147(2): 823–851.

Moneriz, C., J. Mestres, J. M. Bautista, A. Diez and A. Puyet. 2011. Multi-targeted activity of maslinic acid as an antimalarial natural compound. FEBS J. 278(16): 2951–2961.

Mouly, P. P., C. R. Arzouyan, E. M. Gaydou and J. M. Estienne. 1994. Differentiation of citrus juices by factorial discriminant analysis using liquid chromatography of flavanone glycosides. Journal of Agricultural and Food Chemistry 42(1): 70–79.

Muhammad, S. and A. Fatima. 2014. Studies on phytochemical evaluation and antibacterial properties of two varieties of kolanut (*Cola nitida*) in Nigeria. Journal of Biosciences and Medicines 2(2): 37.

Nagaoka, T., T. Yoshihara, J. Ohra and S. Sakamura. 1993. The international journal of plant biochemistry steroidal alkaloids from roots of tomato stock. Phytochemistry 34(4): 1153–1157.

Naumovski, N. 2015. Bioactive Composition of Plants and Plant Foods. Plant Bioactive Compounds for Pancreatic Cancer Prevention and Treatment. C. J. Scarlett and Q. V. Vuong. New York, Nova Publishers: 322.

Naumovski, N., B. L. Blades and P. D. Roach. 2015. Food inhibits the oral bioavailability of the major green tea antioxidant epigallocatechin gallate in humans. Antioxidants 4: 373–393.

Nazaruddin, R., L. K. Seng, O. Hassan and M. Said. 2006. Effect of pulp preconditioning on the content of polyphenols in cocoa beans (*Theobroma cacao*) during fermentation. Industrial Crops and Products 24(1): 87–94.

Nemitz, M. C., F. K. J. Yatsu, J. Bidone, L. S. Koester, V. L. Bassani, C. V. Garcia, A. S. L. Mendez, G. L. von Poser and H. F. Teixeira. 2015. A versatile, stability-indicating and high-throughput ultra-fast liquid chromatography method for the determination of isoflavone aglycones in soybeans, topical formulations, and permeation assays. Talanta 134: 183–193.

Neveu, V., J. Perez-Jimenez, F. Vos, V. Crespy, L. du Chaffaut, L. Mennen, C. Knox, R. Eisner, J. Cruz, D. Wishart and A. Scalbert. 2010. Phenol-explorer: An online comprehensive database on polyphenol contents in foods. Database (Oxford) 2010: bap024.

Newman, R. A., P. Yang, A. D. Pawlus and K. I. Block. 2008. Cardiac glycosides as novel cancer therapeutic agents. Mol. Interv. 8(1): 36.

Nielsen, J. K., C. E. Olsen and M. K. Petersen. 1993. Acylated flavonol glycosides from cabbage leaves. Phytochemistry 34(2): 539–544.

Ong, K. C. and H. E. Khoo. 1997. Biological effects of myricetin. Gen. Pharmacol. 29(2): 121–126.

Orban, N., I. O. Kozak, M. Dravucz and A. Kiss. 2009. LC-MS method development to evaluate major triterpenes in skins and cuticular waxes of grape berries. International Journal of Food Science and Technology 44(4): 869–873.

Ortega, R. 2006. Importance of functional foods in the Mediterranean diet. Public Health Nutr. 9(8A): 1136–1140.

Pereira, R. M., G. Á. Ferreira-Silva, M. Pivatto, L. d. Á. Santos, V. d. S. Bolzani, D. A. Chagas de Paula, J. C. d. Oliveira, C. Viegas Júnior and M. Ionta. 2016. Alkaloids derived from flowers of Senna spectabilis, (−)-cassine and (−)-spectaline, have antiproliferative activity on HepG2 cells for inducing cell cycle arrest in G1/S transition through ERK inactivation and downregulation of cyclin D1 expression. Toxicol. *In Vitro* 31: 86–92.

Petersson, E. V., U. Arif, V. Schulzova, J. Krtková, J. Hajšlová, J. Meijer, H. C. Andersson, L. Jonsson and F. Sitbon. 2013. Glycoalkaloid and calystegine levels in table potato cultivars subjected to wounding, light, and heat treatments. Journal of Agricultural and Food Chemistry 61(24): 5893–5902.

Piccinelli, A. L., A. Veneziano, S. Passi, F. D. Simone and L. Rastrelli. 2007. Flavonol glycosides from whole cottonseed by-product. Food Chemistry 100(1): 344–349.

Piironen, V., D. G. Lindsay, T. A. Miettinen, J. Toivo and A. M. Lampi. 2000. Plant sterols: Biosynthesis, biological function and their importance to human nutrition. Journal of the Science of Food and Agriculture 80(7): 939–966.

Przybylak, J. K., D. Ciesiołka, W. Wysocka, P. M. García-López, M. A. Ruiz-López, W. Wysocki and K. Gulewicz. 2005. Alkaloid profiles of Mexican wild lupin and an effect of alkaloid preparation

from Lupinus exaltatus seeds on growth and yield of paprika (*Capsicum annuum* L.). Industrial Crops and Products 21(1): 1–7.

Ramkissoon, J. S., M. F. Mahomoodally, A. H. Subratty and N. Ahmed. 2016. Inhibition of glucose- and fructose-mediated protein glycation by infusions and ethanolic extracts of ten culinary herbs and spices. Asian Pacific Journal of Tropical Biomedicine 6(6): 492–500.

Reyes, L. F., J. C. Miller and L. Cisneros-Zevallos. 2005. Antioxidant capacity, anthocyanins and total phenolics in purple-and red-fleshed potato (*Solanum tuberosum* L.) genotypes. American Journal of Potato Research 82(4): 271–277.

Romero, C., A. Garcia, E. Medina, M. V. Ruiz-Mendez, A. de Castro and M. Brenes. 2010. Triterpenic acids in table olives. Food Chemistry 118(3): 670–674.

Ruberto, G., A. Renda, C. Daquino, V. Amico, C. Spatafora, C. Tringali and N. D. Tommasi. 2007. Polyphenol constituents and antioxidant activity of grape pomace extracts from five Sicilian red grape cultivars. Food Chemistry 100(1): 203–210.

Sang, S., K. Lapsley, R. T. Rosen and C. -T. Ho. 2002. New prenylated benzoic acid and other constituents from almond hulls (*Prunus amygdalus* batsch). Journal of Agricultural and Food Chemistry 50(3): 607–609.

Santos, P. L., L. N. S. Santos, S. P. M. Ventura, R. L. d. Souza, J. A. P. Coutinho, C. M. F. Soares and Á. S. Lima. 2016. Recovery of capsaicin from *Capsicum frutescens* by applying aqueous two-phase systems based on acetonitrile and cholinium-based ionic liquids. Chemical Engineering Research and Design In press.

Sathyapalan, T., S. Beckett, A. S. Rigby, D. D. Mellor and S. L. Atkin. 2010. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. Nutr. J. 9: 55.

Schieber, A., F. C. Stintzing and R. Carle. 2001. By-products of plant food processing as a source of functional compounds—Recent developments. Trends in Food Science & Technology 12(11): 401–413.

Schieber, A., W. Ullrich and R. Carle. 2000. Characterization of polyphenols in mango puree concentrate by HPLC with diode array and mass spectrometric detection. Innovative Food Science & Emerging Technologies 1(2): 161–166.

Scott, P. M. and A. Lawrence Guillaume. 1982. Losses of ergot alkaloids during making of bread and pancakes. Journal of Agricultural and Food Chemistry 30(3): 445–450.

Shahidi, F. and P. Ambigaipalan. 2015. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects—A review. J. Funct. Food 18, Part B: 820–897.

Shi, Q., S. Hui, Z. Ai-Hua, X. Hong-Ying, Y. Guang-Li, Y. Ying and W. Xi-Jun. 2014. Natural alkaloids: Basic aspects, biological roles, and future perspectives. Chinese J. Nat. Med. 12(6): 401–406.

Soldi, C., M. G. Pizzolatti, A. P. Luiz, R. Marcon, F. C. Meotti, L. A. Mioto and A. R. Santos. 2008. Synthetic derivatives of the alpha- and beta-amyrin triterpenes and their antinociceptive properties. Bioorg. Med. Chem. 16(6): 3377–3386.

Souquet, J. -M., B. Labarbe, C. Le Guernevé, V. Cheynier and M. Moutounet. 2000. Phenolic composition of grape stems. Journal of Agricultural and Food Chemistry 48(4): 1076–1080.

Spatafora, C., E. Barbagallo, V. Amico and C. Tringali. 2013. Grape stems from Sicilian *Vitis vinifera* cultivars as a source of polyphenol-enriched fractions with enhanced antioxidant activity. LWT-Food Science and Technology 54(2): 542–548.

Stalmach, A., S. Troufflard, M. Serafini and A. Crozier. 2008. Absorption, metabolism and excretion of Choladi green tea flavan-3-ols by humans. Mol. Nutr. Food Res.

Stiti, N. and M. A. Hartmann. 2012. Nonsterol triterpenoids as major constituents of Olea europaea. J. Lipids 2012: 476595.

Sujak, A., A. Kotlarz and W. Strobel. 2006. Compositional and nutritional evaluation of several lupin seeds. Food Chemistry 98(4): 711–719.

Sutovsky, P., A. S. Cupp, W. Thompson and M. Baker. 2016. Reproductive systems biology tackles global issues of population growth, food safety and reproductive health. Cell Tissue Res. 363(1): 1–5.

Szakiel, A., C. Paczkowski, F. Pensec and C. Bertsch. 2012. Fruit cuticular waxes as a source of biologically active triterpenoids. Phytochem. Rev. 11(2-3): 263–284.

Teponno, R. B., S. Kusari and M. Spiteller. 2016. Recent advances in research on lignans and neolignans. Nat. Prod. Rep.

Tilman, D., C. Balzer, J. Hill and B. L. Befort. 2011. Global food demand and the sustainable intensification of agriculture. Proc. Natl. Acad. Sci. USA 108(50): 20260–20264.

Tsao, R. 2010. Chemistry and biochemistry of dietary polyphenols. Nutrients 2(12): 1231–1246.

Tunçel, G., M. J. R. Nout and L. Brimer. 1995. The effects of grinding, soaking and cooking on the degradation of amygdalin of bitter apricot seeds. Food Chemistry 53(4): 447–451.

Turner, C., P. Turner, G. Jacobson, K. Almgren, M. Waldebäck, P. Sjöberg, E. N. Karlsson and K. E. Markides. 2006. Subcritical water extraction and β-glucosidase-catalyzed hydrolysis of quercetin glycosides in onion waste. Green Chemistry 8(11): 949–959.

Villasenor, I. M., J. Angelada, A. P. Canlas and D. Echegoyen. 2002. Bioactivity studies on beta-sitosterol and its glucoside. Phytotherapy Research 16(5): 417–421.

Vuong, Q. V., J. B. Golding, M. Nguyen and P. D. Roach. 2010. Extraction and isolation of catechins from tea. J. Sep. Sci. 33(21): 3415–3428.

Vuong, Q. V., J. B. Golding, C. E. Stathopoulos, M. H. Nguyen and P. D. Roach. 2011. Optimizing conditions for the extraction of catechins from green tea using hot water. J. Sep. Sci. 34(21): 3099–3106.

Wallace, T. C. 2011. Anthocyanins in cardiovascular disease. Adv. Nutr. 2(1): 1–7.

Wan, X., D. Li and Z. Zhang. 2009. Antioxidant properties and mechanisms of tea polyphenols. pp. 131–160. *In*: T. C. Ho, J. K. Lin and F. Shahidi (eds.). Tea and Tea Products: Chemistry and Health Promoting Properties. Boca Raton, FL, CRC Press.

Wang, G. -W., W. -T. Hu, B. -K. Huang and L. -P. Qin. 2011. *Illicium verum*: A review on its botany, traditional use, chemistry and pharmacology. Journal of Ethnopharmacology 136(1): 10–20.

Wang, K., A. Li, R. Zhang, S. Li, F. Zhang, L. Zhao, Z. Zhao, S. Li, J. Cai and J. Cao. 2016. Five new steroidal glycosides from the roots of *Cynanchum stauntonii*. Phytochem. Lett. 16: 178–184.

WHO. 2014. Global status report on noncommunicable diseases 2014. 2015, from http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf?ua=1.

Williams, P. J., C. R. Strauss, B. Wilson and R. A. Massy-Westropp. 1983. Glycosides of 2-phenylethanol and benzyl alcohol in *Vitis Vinifera* grapes. Phytochemistry 22(9): 2039–2041.

Wolfe, K. L. and R. H. Liu. 2003. Apple peels as a value-added food ingredient. J. Agric. Food Chem. 51(6): 1676–1683.

Wu, C. D. 2009. Grape products and oral health. J. Nutr. 139(9): 1818S–1823S.

Yadav, M., S. Jain, A. Bhardwaj, R. Nagpal, M. Puniya, R. Tomar, V. Singh, O. Parkash, G. B. K. S. Prasad, F. Marotta and H. Yadav. 2009. Biological and medicinal properties of grapes and their bioactive constituents: An update. Journal of Medicinal Food 12(3): 473–484.

Yahara, S., N. Uda, E. Yoshio and E. Yae. 2004. Steroidal alkaloid glycosides from tomato (*Lycopersicon esculentum*). Journal of Natural Products 67(3): 500–502.

Yamaguchi, H., T. Noshita, Y. Kidachi, H. Umetsu, M. Hayashi, K. Komiyama, S. Funayama and K. Ryoyama. 2008. Isolation of ursolic acid from apple peels and its specific efficacy as a potent antitumor agent. Journal of Health Science 54(6): 654–660.

Young, J. E., X. Zhao, E. E. Carey, R. Welti, S. -S. Yang and W. Wang. 2005. Phytochemical phenolics in organically grown vegetables. Molecular Nutrition & Food Research 49(12): 1136–1142.

Zhang, J., J. Chen, Z. Liang and C. Zhao. 2014. New lignans and their biological activities. Chem. Biodivers. 11(1): 1–54.

Zhang, Y. J., B. Jayaprakasam, N. P. Seeram, L. K. Olson, D. DeWitt and M. G. Nair. 2004. Insulin secretion and cyclooxygenase enzyme inhibition by Cabernet Sauvignon grape skin compounds. Journal of Agricultural and Food Chemistry 52(2): 228–233.

Zotchev, S. B. 2013. Alkaloids from Marine Bacteria. Advances in Botanical Research. G. -G. Nathalie, Academic Press 68: 301–333.

Phenolic Compounds
Potential Health Benefits and Toxicity

Deep Jyoti Bhuyan[1,*] and *Amrita Basu*[2]

Introduction

Phenolic compounds are probably the most explored natural compounds due to their potential health benefits as demonstrated in a number of studies (Del Rio et al. 2010). Generic terms 'phenolic compounds', 'phenolics' or 'polyphenolics' refer to more than 8,000 compounds found in the plant kingdom and possessing at least an aromatic ring with one or more hydroxyl substituents, including functional derivatives like esters, methyl ethers, glycosides, etc. (Ho 1992, Cartea et al. 2011). These are plant secondary metabolites produced via shikimic acid pathway (Cartea et al. 2011, Talapatra and Talapatra 2015). Phenolic compounds regulate the various metabolic functions including structure and growth, pigmentation and are resistant to different pathogens in plants (Naumovski 2015). The organoleptic properties of the plant food (fruits, vegetables, cereals, legumes, etc.) and beverages (tea, coffee, beer, wine, etc.) are also partially ascribed to phenolic compounds (Dai and Mumper 2010). For instance, the interactions between phenolic compounds (such as procyanidins) and the glycoprotein present in our saliva contribute to the bitterness and astringency of fruit and juices (Dai and Mumper 2010). These phenolics have varied chemical structures ranging from simple molecules (i.e., phenolic acids) to more complex polymerized compounds (i.e., proanthocyanidins) (Galleano et al. 2010). They also help in defense against ultraviolet radiation, insects and predators (Dai and Mumper 2010). Phenolics derived from various natural sources are linked to antioxidant, anti-inflammatory, anti-allergic, anti-carcinogenic, antihypertensive, cardioprotective, anti-arthritic and antimicrobial activities (Rauha et al. 2000, Penna et al. 2001, Puupponen-Pimia et al. 2001, Wang and Mazza 2002, Liu et al. 2004, Dai and Mumper 2010). Studies

[1] Researcher and Casual Academic, Pancreatic Cancer Research Group, School of Environmental & Life Sciences, University of Newcastle, 10 Chittaway Rd., Ourimbah, NSW 2258, Australia.

[2] Research Centre for Toxic Compounds in the Environment, Masaryk University, Brno, Czech Republic.

* Corresponding author: deepjyoti.bhuyan@uon.edu.au

on natural antioxidants has developed significantly in the last few years due to restrictions on the use of synthetic antioxidants and enhanced public awareness of health-related issues (Vázquez et al. 2012). Because of their potential health benefits, natural antioxidants are considered to be a better alternative than the synthetic ones (Fu et al. 2010). Hence, the identification of novel antioxidants from natural sources is one of the main research focuses in natural product development these days. Various studies validate the positive correlation between phenolic content and the antioxidant activity (Dimitrios 2006, Galleano et al. 2010, Bhuyan et al. 2015). Free radicals play an important role in the development of cancer, diabetes, neurodegenerative, ageing-related and cardiovascular diseases. Therefore, antioxidants, such as flavonoids and other phenolics have gained more attention in recent years as potential agents for preventing and treating a number of oxidative stress-related and chronic diseases (Rice-Evans et al. 1996, Stanner et al. 2004, Dimitrios 2006, Fu et al. 2010, Galleano et al. 2010, Gharekhani et al. 2012). The antioxidant activity of phenolics is primarily attributed to their redox properties that enable them to act as singlet oxygen quenchers, reducing agents and hydrogen donors (Rice-Evans et al. 1996, Galleano et al. 2010, Gharekhani et al. 2012). The hydroxyl (–OH) groups of phenolics are good H-donating antioxidants that disrupt the cycle of new radical generation by scavenging reactive oxygen species (ROS) (Castellano et al. 2012).

Types of Phenolic Compounds

The basic structure of a phenolic compound comprises of an aromatic ring with one or more –OH groups. However, phenolic compounds found in Nature are structurally diverse from simple phenolic molecules to complex polymerized compounds (Balasundram et al. 2006). Phenolics found in food material can be divided into three major groups: simple phenols and phenolic acids, hydroxycinnamic acid derivatives and flavonoids (Ho 1992). In addition, based on the number of carbons, the phenolic compounds commonly found in plants can be classified into several groups (Harborne 1989, Baxter et al. 1998, Robards et al. 1999, Balasundram et al. 2006) as shown in Table 1. Phenolic acids, flavonoids and tannins are considered as the main dietary phenolics (King and Young 1999, Balasundram et al. 2006). Flavonoids constitute the largest group of low-molecular-weight plant phenolics and have been studied most extensively (King and Young 1999). They are also the most important plant pigments. Over 4,000 different types of flavonoids are found in Nature (Harborne 1989, Craig 1999). Flavonoids usually occur bound to sugar molecules and consist mainly of catechins, proanthocyanins, anthocyanidins, flavons and flavonols and their glycosides (Ho 1992, King and Young 1999). According to the degree of hydroxylation and the presence of a C2–C3 double-bond in the heterocyclic pyrone ring, flavonoids can be divided into 13 classes (González 2002) and the most important ones are flavonols, flavones, isoflavones, anthocyanidins or anthocyanins and flavanones (Scalbert and Williamson 2000). Flavon-3-ols are most dominant in different kinds of tea (*Camellia sinensis*), berries, cherries, grapes, plums, apricots, red wine and chocolate (Lotito and Frei 2006, D'Archivio et al. 2007, Ratnasooriya et al. 2010). Anthocyanins are natural pigments in plants and exhibit blue, purple or red color (D'Archivio et al. 2007, Wojdylo et al. 2008). These compounds are abundant in purple berries, apples, cherries, red and purple grapes and pomegranates, red wine and certain vegetables,

Table 1. Classification of phenolic compounds.

Class	Number of carbon atoms	Basic structure	Examples
Simple phenolics Benzoquinones	6	C_6	Catechol, hydroquinone 2,6-Dimethoxybenzoquinone
Phenolic acids	7	C_6–C_1	Gallic, salicylic acids
Acethophenones Phenylacetic acids	8	C_6–C_2	3-Acetyl-6-methoxybenzaldehyde p-Hydroxyphenylacetic acid
Hydroxycinnamic acids Phenylpropanoids Coumarins Isocoumarins Chromones	9	C_6–C_3	Caffeic, ferulic acids Myristicin, eugenol Umbelliferone, aesculetin Bergenin Eugenin
Napthoquinones	10	C_6–C_4	Juglone, plumbagin
Xanthones	13	C_6–C_1–C_6	Mangiferin
Stilbenes Anthraquinones	14	C_6–C_2–C_6	Lunularic acid, resveratrol Emodin
Flavonoids Isoflavonoids	15	C_6–C_3–C_6	Quercetin, cyaniding Genistein
Lignans Neolignans	18	$(C_6$–$C_3)_2$	Pinoresinol Eusiderin
Biflavonoids	30	$(C_6$–C_3–$C_6)_2$	Amentoflavone, agathisflavone
Lignins	many	$(C_6$–$C_3)n$	Pinoresinol
Condensed tannins (proanthocyanidins or flavolans)	many	$(C_6$–C_3–$C_6)n$	Selligueain A, prodelphinidin

such as cabbage, onions and radish (Manach et al. 2004, D'Archivio et al. 2007, de Pascual-Teresa et al. 2010). Some examples of flavanones are: eriodictyol, hesperetin and naringenin. These compounds are commonly found in citrus fruits and to a lesser extent in tomatoes and mint (Manach et al. 2004, D'Archivio et al. 2007). They can also be seen in green leafy herbs, like parsley and chamomile. Flavanones comprise of the smallest group of compounds, starting with glycosides of naringenin which is present in grapefruit followed by hesperetin that is present in oranges (D'Archivio et al. 2007).

Phenolic acids are divided into two subgroups: hydroxybenzoic and hydroxycinnamic acids (Balasundram et al. 2006). Phenolic acids are significant components of fruit and vegetables. These compounds play an important role in color stability, aroma profile and antioxidant activity. They act as acids because of their carboxylic group (Fleuriet and Macheix 2003). Ellagic and gallic acids are two major dietary hydroxybenzoic acids in berries and nuts (Maas et al. 1991, King and Young 1999). Caffeic, ferulic, *p*-coumaric and sinapic acids are the most common hydroxycinnamic acids and aromatic in Nature (Bravo 1998, Balasundram et al. 2006). Chlorogenic acid is an important member of this group with regard to food material

and is the key substrate for enzymatic browning of fruits, such as apples and pears (Eskin 1990, Ho 1992). Chlorogenic acid is commonly found in higher quantities in seeds, such as coffee beans, sunflower seeds and grains and is formed when caffeic acid is combined with quinic acid (Sondheimer 1958, King and Young 1999).

Tannins are the third important group of polyphenolics which can further be divided into two subcategories: condensed and hydrolysable tannins (Porter 1989). These are high-molecular-weight polymers. Fruits, grains and legumes consist of condensed tannins which are mainly polymers of catechins or epicatechins, whereas hydrolysable tannins are polymers of gallic or ellagic acid and found in berries and nuts (King and Young 1999). Condensed tannins are also known as proanthocyanidins and polyflavonoid, consisting of chains of flavan-3-ol units. They usually accumulate in the outer layers of plants (Ho 1992, King and Young 1999).

Potential health benefits

For centuries, plants and plant-derived products have played a key role in maintenance of human health by improving the quality of life (Craig 1999). Numerous studies have reported the potential health benefits of plant polyphenolics in particular. Due to their potent antioxidant properties, plant phenolics have scientifically proven to prevent various oxidative stress-related as well as chronic diseases, such as cancer, cardiovascular and neurodegenerative diseases. In spite of their wide distribution in the plant kingdom, researchers have directed their attention to the health benefits of phenolics only now (Dai and Mumper 2010).

Cancer

Oxidative stress plays an important role in carcinogenesis. Several mechanisms contribute to the overall formation of tumours from oxidative damage. Free radicals induce oxidative stress, which leads to DNA damage in the cell, which, in turn, can lead to base mutation, single and double strand breaks, DNA cross-linking and chromosomal abnormality, if left unrepaired (Liu 2003). Therefore, phenolics with antioxidant properties have been found to be beneficial in preventing or treating the oxidative damage that can induce cancer. In addition to antioxidant properties, polyphenols also modulate the activity of a number of enzymes and cell receptors, indicating other specific biological actions in prevention and treatment of several diseases, including cancer (Dai and Mumper 2010). For instance, different phenolic compounds associate with the regulation of gene expression in cell proliferation and apoptosis, both *in vitro* and *in vivo*. Several *in vitro* and *in vivo* studies show that flavonoids may interrupt different stages of carcinogenesis not only with antioxidant activity but also with other anticancer mechanisms (Hollman et al. 1996, Rice-Evans and Miller 1996, Tham et al. 1998, Yang et al. 2001, Kris-Etherton et al. 2002). Polyphenols may affect the molecular events in the initiation, promotion and progression stages of carcinogenesis and isoflavones and lignans may affect the estrogen-related activities related to tumour formation (Yang et al. 2001). Flavonoids have been reported to modulate key enzymes and receptors involved in signal transduction pathways of cellular proliferation, differentiation, apoptosis, inflammation, angiogenesis, metastasis and reversal of multidrug resistance (Ravishankar et al. 2013). Programmed cell death, commonly

known as apoptosis, is required to maintain a balance between cell proliferation and cell loss (Zuzana 2011). Misregulation of this balance can lead to malignant transformation, whereas induction of apoptosis suppresses the development of cancer (Tang and Porter 1996, Bhat and Pezzuto 2002). Compounds, such as resveratrol, have shown to induce apoptosis in malignant cells and provide a promising natural strategy to prevent cancer (Katdare et al. 1999, Surh et al. 1999).

Loo (2003) suggested that highly invasive or metastatic cancer cells may require a specific amount of oxidative stress for maintaining their proliferation or apoptosis. Therefore, they generate high yet tolerable amounts of H_2O_2 (hydrogen peroxide) which act as signaling molecules (in the mitogen-activated protein kinase pathway) to activate redox-sensitive transcription factors and responsive genes. These transcription factors and genes are involved in the survival and proliferation of cancer cells. Loo (2003) also proposed that polyphenols with antioxidant capacity can either scavenge the H_2O_2 produced by the cancer cells or certain polyphenols (such as EGCG, quercetin and gallic acid) can induce the formation of H_2O_2 to achieve an intolerable level of high oxidative stress in cancer cells to inhibit their proliferation. Gopalakrishnan and Tony Kong (2008) suggested that phytochemicals, such as polyphenols, protect normal cells by Nrf2 which plays a key role in antioxidant response elements (ARE)-driven gene expression and on the other hand, modulate the transcription factors nuclear factor κB (NFκB) and AP-1 in abnormal cancer cells, which lead to cytotoxicity. Phenolics can modulate various components of the epigenetic machinery in humans (Link et al. 2010). These modulations include the changes in DNA methylation pattern, histone modifications and the expression of some non-coding miRNAs which lead to activation of tumor-suppressor genes and inactivation of oncogenes. Modulation of cytochrome p450 expression is another proposed anticancer mechanism of action of polyphenols. Cytochrome p450 mixed-function oxidases play an important role in the metabolic activation of chemical carcinogens. Phenolic compounds are hypothesized to stimulate cytochrome p450-conjugating enzymes with the ability to metabolically inactivate the chemical carcinogens produced by the mixed function oxidases (Vuong et al. 2014).

Many plant-derived phenolic compounds, for instance, tea polyphenols (green tea), gingerol (gingers), resveratrol (grapes), curcumin (turmeric), genistein (soybean), rosmarinic acid (rosemary), apigenin (parsley) and silymarin (milk thistle) are used in conjunction with chemotherapy and radiation therapy (Wang et al. 2012). Gingerol, a major phenolic compound derived from ginger (*Zingiber officinale*) and its derivative 6-shogaol have been found to possess anticancer activity against oral, kidney, lung, brain and breast cancer cells (Chen et al. 2008, Chen et al. 2010, Han et al. 2015, Lee et al. 2014, Hsu et al. 2015). The latter can induce stress in cancer cells by increasing cytosolic Ca^{2+} levels and cause apoptotic cell death of both human oral cancer cells and renal tubular cells (Chen et al. 2008, 2010).

The role of the flavonoid, quercetin, in anticancer research has been emphasized in a number of reports (Kris-Etherton et al. 2002). Quercetin is the most abundant flavonoid found in fruits after keamferol and myricetin (Vuong et al. 2014). The antioxidant activity of quercetin is well established as the most potent scavenger of ROS (superoxide) and reactive nitrogen species (nitric oxide and peroxynitrite) (Boots et al. 2008, Vuong et al. 2014). An *in vivo* study by Jin et al. (2006) revealed that quercetin had a significant preventive effect on benzo[a]pyrene-induced DNA

damage along with a potential chemopreventive effect on the benzo[a]pyrene-induced carcinogenesis of lung cancer. The inhibition of cytochrome p4501A1 activity might be the possible mechanism of these effects of quercetin. Quercetin was also found to inhibit the matrix metalloproteinase-3 (MMP-3) activity and invasion of the MDA-MB-231 human breast carcinoma cell line (Phromnoi et al. 2009) and HGF/Met signaling in medulloblastoma cell line (Labbe et al. 2009).

Another dietary flavonoid—keamferol (also known as kaempferol), a type of phytoestrogen found in a number of fruits and vegetables—is shown to promote human health by reducing the risk of chronic diseases, especially cancer (Chen 2013, Kim and Choi 2013, Lee and Kim 2016). It is reported to regulate major elements of cellular signal transduction pathways associated with apoptosis, angiogenesis, inflammation and metastasis (Zhang et al. 2008, Chen and Chen 2013, Lee and Kim 2016). The anticancer effect of kaempferol in MIA PaCa-2, PANC-1, and SNU-213 human pancreatic cancer cells is mediated by inhibition of EGFR related Src, ERK1/2, and AKT pathways (Lee and Kim 2016). Furthermore, kaemferol is reported to inhibit the migration and invasion ability of medulloblastoma (Labbe et al. 2009) and breast cancer cells (Phromnoi et al. 2009).

Myricetin has been broadly studied to investigate its anticancer properties and mechanisms of action against different types of cancer (Maggiolini et al. 2005, Lu et al. 2006, Kumamoto et al. 2009, Sun et al. 2012, Devi et al. 2015). For instance, in human colon cancer cells, myricetin induces cell death via BAX/BCL2-dependent pathway (Kim et al. 2014), whereas in the colorectal carcinoma cells, it inhibits MMP-2 protein expression and enzyme activity (Ko et al. 2005). It also acts as an agonist for estrogen receptor alpha which leads to inhibition of hormone-dependent MCF7 breast-cancer cell proliferation (Maggiolini et al. 2005). Additionally, myricetin interacts with a number of oncoproteins, such as protein kinase B (PKB) (AKT), Fyn, MEK1, and JAK1–STAT3 (Janus kinase–signal transducer and activator of transcription 3), and reduces the neoplastic transformation of cancer cells (Kumamoto et al. 2009, Sun et al. 2012, Devi et al. 2015). Lu et al. (2006) showed that the plant flavonoids—quercetin and myricetin, inhibit thioredoxin reductase (TrxR) (which is overexpressed in many aggressive tumors) that induces cell death.

Apigenin, a flavone abundantly found in fruits and vegetables, is shown to possess anticancer properties against cancer of breast, cervix, colon, leukemia, lung, ovarian, prostate, skin, thyroid, gastric, liver and neuroblastoma, to name a few (Shukla and Gupta 2010). A study by Ruela-de-Sousa et al. (2010) suggested that apigenin can block proliferation in two types of leukemia cells—myeloid and erythroid subtypes through cell-cycle arrest in G_2/M phase (myeloid HL60) and G_0/G_1 phase (erythroid TF1 cells). Choudhury et al. (2013) also showed that apigenin and curcumin can synergistically induce cell death and apoptosis and block cell cycle progression at G_2/M phase of A549 lung epithelium cancer cells. They also established that both apigenin and curcumin can simultaneously bind at different sites of tubulin. Similarly, apigenin is also linked with inhibition of pancreatic cancer cell proliferation by G_2/M cell cycle arrest, down regulation of the overexpressed protein geminin, increase in growth inhibitory effects of gemcitabine and abrogation of gemcitabine resistance in multiple reports (Ujiki et al. 2006, Salabat et al. 2008, Strouch et al. 2009). Another study by Gomez-Garcia et al. (2013) demonstrated that both potassium apigenin and carnosic acid have chemoprotective effects against 7,12-dimethyl benzanthracene

(DMBA)-induced carcinogenesis in hamster. Moreover, the anti-proliferative and anti-angiogenic effects of the flavonoid, apigenin, were illustrated by Melstrom et al. (2011). They established that apigenin inhibits HIF-1α, GLUT-1, and VEGF mRNA and protein expression in pancreatic cancer cells in both normoxic and hypoxic conditions, proving its potential as a therapeutic agent for pancreatic cancer. Johnson et al. (2011) showed that citrus flavonoids, such as luteolin, apigenin and quercetin can inhibit glycogen synthase kinase-3β (GSK-3β), which leads to decreased cancer cell proliferation and survival by reducing NFκB activity. They made similar observations *in vivo*. Apigenin and luteolin were also shown to improve the efficacy of certain chemotherapeutic drugs—gemcitabine, cisplatin, 5-fluorouracil and oxaliplatin—in terms of their anti-proliferative activity against BxPC-3 human pancreatic cancer cells by Johnson and Gonzalez de Mejia in 2013. Moreover, Lee et al. (2008) made similar observations and proposed that gemcitabine in combination with apigenin resulted in enhanced apoptosis and growth inhibition by down-regulation of NFκB activity through suppression of AKT activation in pancreatic cancer cell lines *in vitro*.

Other phenolic compounds, such as catechin, epicatechin, epigallocatechin-3-gallate (EGCG), nariganin, chalcones, daidzein, gallic acid, protocatechuic acid (PCA), caffeic acid, genistein, stilbenes and anthocyanins were also investigated for their anticancer mechanisms against different types of cancer cell lines (Chahar et al. 2011, Li et al. 2013, Vuong et al. 2014).

An inverse relation between the consumption of flavonoid and risks for certain types of cancer was demonstrated in many epidemiologic studies (Kris-Etherton et al. 2002). A study of 9,959 men and women aged 15–99 years, in Finland, was conducted to demonstrate the relation between the intake of flavonoids and subsequent risk of cancer (Knekt et al. 1997). This study observed an inverse association between flavonoid intake and incidence of all the sites of cancer combined. The risk of lung cancer was reduced with flavonoid intake as found in the 24-year follow-up study. Another study conducted in Finland with a cohort of 27,110 male smokers aged 50–69 years without history of cancer, revealed that the intake of flavonols and flavones can be inversely associated with the risk of lung cancer, but not with that of other cancers (Hirvonen et al. 2001). Likewise, statistically significant inverse associations between the food sources rich in flavonoids quercetin (onions and apples) and naringin (white grapefruit) and lung cancer risk were observed by Le Marchand et al. (2000).

Cardiovascular diseases

Cardiovascular disease (CVD) is one the major killers in all developed countries with a rise in prevalence (Rangel-Huerta et al. 2015, Tome-Carneiro and Visioli 2016). Polyphenols from foods, such as tea, coffee, cocoa, olive oil, red wine and many fruits and vegetables were studied extensively to evaluate their effect on CVD risk (Tangney and Rasmussen 2013). Several epidemiologic studies and intervention trials suggest that polyphenols present in fruits and vegetables are associated with decreased risk of cardiovascular diseases (Morton et al. 2000, Kris-Etherton et al. 2002, Vita 2005, Tangney and Rasmussen 2013, Rangel-Huerta et al. 2015, Tome-Carneiro and Visioli 2016). Oxidative stress may play a role in the pathogenesis of CVD, like atherosclerosis (Morton et al. 2000). As polyphenols are known for their antioxidant activities, increased intake of dietary antioxidants may protect against