REVIEW ARTICLE

IJVAR *International Journal of Veterinary and Animal Research*
E-ISSN: 2651-3609 4(3): 115-121, 2021

Phenolic Compounds for Drug Discovery: Potent Candidates for Anti-cancer, Anti-diabetes, Anti-inflammatory and Anti-microbial

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Received: June 24, 2021
Accepted: July 29, 2021

Abstract

Due to the ubiquitous nature of phenolics and their well-documented health benefits, they have great potentials for drug development. Thus, this review sought to add to existing literature regarding the anti-cancer, anti-diabetic, anti-inflammatory, and anti-microbial potentials of phenolic compounds mainly, phenolic acids and flavonoids. Hence, ensuring a good balance between reactive species; reactive oxygen species (ROS) and reactive nitrogen species (RNS), and anti-oxidants via the consumption of diets rich in phenolic compounds is crucial for the prevention of oxidative stress-related diseases. Aside from that, consuming phenolics reduces one's risk of contracting microbial-borne diseases as they possess an anti-microbial potential. Consequently, phenolic compounds are potent candidates for drug development. However, further studies should be conducted to elucidate their anti-cancer, anti-diabetic, anti-inflammatory, and anti-microbial mechanisms. Also, new studies should be carried to elucidate the efficacies of phenolic compounds-metal complexes in anti-cancer, anti-diabetic, anti-inflammatory, and anti-microbial.

Keywords: Anti-cancer, Anti-diabetes, Anti-inflammatory, Anti-microbial and Phenolic compounds.

INTRODUCTION

Epidemiologically, evidence suggests that diets rich in anti-oxidants reduce susceptibility to oxidative stress-related diseases such as cancer, diabetes and cardiovascular diseases (Kumar and Goelb, 2019). Herbs have been consumed as food and used for medicinal purposes since time immemorial. In recent times, there has been a focus on medicinal herbs including herbs with hypolipidemic, anti-cancer or immune-stimulating properties as they may be useful in reducing the risk of cardiovascular diseases and cancer. These herbs have a wide variety of active phytochemicals including terpenoids, carotenoids, curcumins, and phenolics (Craig, 1999). This anti-oxidant effect of most fruits and vegetables have been attributed to the presence of phenolic compounds such as phenolic acids and flavonoids rather than the presence of vitamin C and vitamin E (Bors et al., 1990; Wang et al., 1996; Tsao and Deng, 2004). Phenolics, which are regarded as an essential component of the human diet, provide other health benefits in addition to their tremendous anti-oxidant activities. However, these compounds manifest variations in their anti-oxidant potentials owing to differences in the number and position of their hydroxyl groups (Kumar and Goelb, 2019).

Plant phenolics including phenolic acids, flavonoids and stilbenes are secondary metabolites emanating mainly from primary metabolites via the shikimate pathway (Kumar and Goelb, 2019; Abotaleb et al., 2020) principally for their numerous benefits to plants such as protection against ultraviolet damage, protection from viruses, insects, provision of smell, color and flavor to plant produce (Griesbach, 2005; Heleno et al., 2015). Phenolics also enhance growth, pigmentation and reproduction (Rosa et al., 2016; Anantharaju et al., 2016; Abotaleb et al., 2020). Phenolic compounds have been grouped into five main classes; stilbenes, tannins, flavonoids, benzoic and cinnamic acids (Anantharaju et al., 2016) (Figure 1).

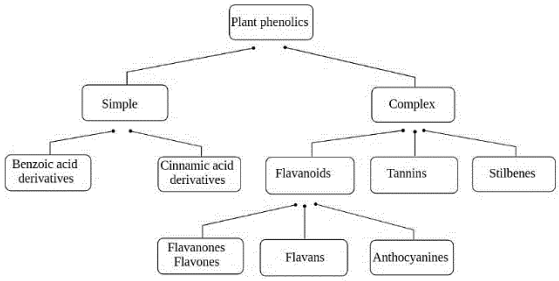

Figure 1. Classification of phenolic compounds. This was adopted from Anantharaju et al. (2016).

Due to the ubiquitous nature of phenolics and their well-documented health benefits such as anti-cancer, anti-inflammatory, anti-microbial and anti-mutagenic; they have great potentials for drug discovery (Kumar and Goelb, 2019; Kumar et al., 2019). Thus, this review sought to evaluate literature regarding the anti-cancer, anti-diabetic and anti-microbial potentials of phenolic compounds mainly, phenolic acids and flavonoids.

Phenolic Acids

Phenolic acids are a subclass of plant phenolic compounds with a single carboxyl group. They are found in plant-based foods viz. skins of fruits, seeds and leaves of vegetables (Pereira et al., 2009). Phenolic acids are

grouped mainly as hydroxybenzoic and hydroxycinnamic acids (Clifford, 1999; Anantharaju et al., 2016). They possess a phenol moiety and a resonance stabilized structure which contributes to their anti-oxidant properties (Kumar and Goelb, 2019) and their anti-oxidant properties have been considered to be much greater than that of well-known anti-oxidant vitamins (Tsao and Deng, 2004; Wang et al., 1996). For instance; the inhibition of cellular ROS in hydrogen peroxide (H_2O_2) treated BNLCL2 cells by vanillic acid exceed that of ascorbic acid (vitamin C) or Trolox (Chou et al., 2010). These compounds exhibit their anti-oxidant activities by either quenching radicals via electron donation or by quenching singlet oxygen (Kumar and Goelb, 2019).

Flavonoids

Flavonoids are complex phenolic compounds, having polyphenolic structures found in vegetables, fruits, bark, roots, flowers, cocoa, tea and wine (Panche et al., 2016). They have a low molecular weight and are widely distributed in the plant kingdom (Dewick, 2001). In vegetables, they are used primarily for growth and for defence against plaque (Havsteen, 2002). In addition, flavonoids provide the color and aroma of flowers. They also play a role in plant pollination by attracting pollinators (Griesbach, 2005). They shield plants from various biotic and abiotic stresses and also serve as unique filters of ultraviolet light in plants (Takahashi and Ohnishi, 2004). Flavonoids play a role in the acclimatization of plants to heat, plants tolerance to freezing, tolerance to drought, and also function as signaling molecules, detoxifying and anti-microbial agents in plants (Samanta and Das, 2011).

Aside from that, flavonoids are believed to have positive effects on both human and animal health and there is interest in their disease therapy and chemoprevention properties (Jorgensen, 1995). Flavonoids have protective effects against human diseases (Kumar and Pandey, 2013) and well-known health benefits and efforts are being made to extract or isolate them. Due to the benefits of flavonoids, their applications in various industries including pharmaceutical, nutraceutical, medicinal and cosmetic is regarded as an indispensable component (Panche et al., 2016). Panche et al. (2016) further added that the wide application of flavonoids is a result of their anti-oxidative, anti-inflammatory, anti-carcinogenic properties and their ability to modulate essential cellular activities of enzymes. These secondary plant metabolites have also been reported to be potent inhibitors of enzymes such as xanthine oxidase (XO) (Hayashi et al., 1988), phosphoinositide 3-kinase (walker et al., 2000), lipoxygenase and cyclo-oxygenase (COX) (Panche et al., 2016).

Flavonoids are grouped according to the carbon in the C ring to which the B ring is attached. Those with their B rings attached to the fourth (4^{th}) carbon of the C ring are neoflavonoids. The attachment of the B ring to the third (3^{rd}) carbon of the C ring brings forth the group termed iso-flavones. However, those with their B rings attached to the second (2^{nd}) carbon of the C ring can be further divided based on the structural features of the C ring as; flavones, flavanones, flavonols, flavanonols, flavanols or catechins, anthocyanins and chalcones. Research on flavonoids has increased following the discovery of their potential to reduce cardiovascular-related diseases and prevent coronary heart diseases (CHD) (Panche et al., 2016).

Phenolic Compounds as Anti-cancer agents

Cancer is characterized by uncontrolled or unlimited cell proliferation (Lee et al., 2017; Akanbong et al., 2021). Cancer is the second global leading cause of death (Abotaleb et al., 2020) and 15.5 million people in the world are estimated to be cancer patients by 2030. Out of these cases, 11.5 million are expected to be fatal (Amin et al., 2009). Conventional approaches mainly, chemotherapy and radiotherapy have been adopted in its treatment. Nonetheless, these treatments have various deleterious effects and disadvantages. Inquest for safer and effective treatments, there is currently interest in plant-derived natural compounds which phenolics have gained importance as potential anti-cancer compounds (Abotaleb et al., 2020).

Populations that consume diets high in food of plant origins such as fruits including berries and nuts, various types of tea, vegetables and spices tend to have a significantly lower incidence of cancer cases, unlike industrialized Western populations. Monophenolic and polyphenolic compounds from a variety of plant foods, spices and beverages have been demonstrated to inhibit the initiation, progression and spread of cancers both *in vitro* and *in vivo* (Table. 1). The cellular mechanism of anti-cancer modulation by phenolics is multi-faceted. It involves the regulation of growth factor-receptor interactions and the cascade of cell signals that determine the expression of genes responsible for cell cycle arrest, maintaining cell survival or responsible for initiating apoptosis (programmed cell death). Phenolics are capable of enhancing the immune system to recognize and destroy cancer cells and also, they can mitigate the growth of new blood vessels (angiogenesis) which is vital for cancer spread. Phenolics have also been reported to have an anti-metastatic potential as they reduce the adhesive and invasive potential of cancer cells (Wahle et al., 2010).

Table 1. Phenolic compounds and their anti-carcinogenic effects.

Phenolic Compound	Type of Cancer	Mode of Action	Reference
	Human Colon Cancer (HCT116 Cells)	Inhibition of angiogenesis and cell proliferation by inhibiting the synthesis of HIF-1α protein	Gong et al. (2019)
Vanillic Acid	Endometrial Carcinoma in Rat Models	Apoptosis, anti-metastasis and anti-oxidant	Bhavani et al. (2017)
	Hepatoma Cells (HTC)	Anti-mutagenic	Almeida et al. (2016)
	Lung and Colon Cancer	Anti-metastasis	Bouzaiene et al. (2015)
Caffeic Acid	Colorectal Cancer Cells	Anti-cancer	Chiang et al. (2014)
	Human Breast CancerCells	Anti-proliferative	Kampa et al. (2004)

Table 1. (Continued)

Phenolic Compound	Type of Cancer	Mode of Action	Reference
Ferulic Acid	Lung and Colon Cancer	Anti-metastasis and Apoptosis	Bouzaiene et al. (2015)
	Osteosarcoma	Inhibition of proliferation and induction of apoptosis	Wang et al., (2016), Zhang et al. (2017)
	Human Breast Cancer Cells	Anti-proliferative	Kampa et al. (2004)
p-Coumaric	Lung and Colon Cancer	Anti-metastasis	Bouzaiene et al. (2015)
Gallic Acid	Pancreatic Cancer	Apoptosis	Liu et al. (2012)
	Gastric Adenocarcinoma Cells	Anti-metastasis	Ho et al. (2010)
Sinapic Acid	HEp-2 Cell Line	Anti-oxidant and Apoptotic	Abdel Rahman et al. (2020)
	Head and Neck Squamous Cell Carcinoma	Apoptotic and changes cancer cell morphology	Rahman et al. (2019)
Quercetin	Lung and Colon Cancer	Anti-cancer and Anti-proliferative	Badr et al. (2019)
	Human Laryngeal Carcinoma Cell Line	Anti-cancer	Janakiraman et al. (2015)
	Human Leukemia Cell Lines (U937 and HL-60)	Apoptosis	Cheng et al. (2010)
	Mesothelioma Cell Lines (SPC212 and SPC111)	Anti-proliferative	Demiroglu-Zergeroglu et al. (2010)
	Prostate Cancer Cell Line (PC-3)	Apoptosis	Senthilkumar et al. (2010)
	Human Oral Squamous Carcinoma/Tongue Cells (SCC-9)	Necrosis and Apoptosis	Haghiac and Walle (2009)
	Colon Cancer Cell Line (Caco-2)	Anti-carcinogenic	Van Erk et al. (2005)
	Human Pancreatic Carcinoma Cell Line (Mia PACA-229) and Rat Pancreatic Carcinoma Cell Line (BSp73AS)	Decreased primary cancer growth, increased apoptosis and also prevented metastasis.	Mouria et al. (2002)
Syringic Acid	Colorectal Cancer	Inhibition of tumor growth and incidence.	Mihanfar et al. (2021)

Recently, there has been a focus on the inhibitory effects of phenolics on the orchestration of gene expressions by stress-activated nuclear factor κB (NF-κB) and activator protein 1 (AP-1) in cancer cells (Wahle et al., 2010).

Phenolic Compounds in Anti-diabetes

Oxidative stress emerging as a result of an imbalance between ROS and anti-oxidants causes metabolic disorders including diabetes. These anti-oxidants hinder the detrimental effects of ROS by scavenging (Furukawa et al., 2017) thus, anti-oxidants are essential in the prevention of diabetes. Phenolic compounds possess high free radicals scavenging potentials (Wu et al., 2014) implying that they possess high anti-diabetes potentials. Also, phenolics are vital in the modulation of blood glucose levels. Phenolic compounds regulate glucose homeostasis by inhibiting carbohydrate digestion and glucose absorption from the intestine via the inhibition of the activities of α-glucosidase and α-amylase (Nwosu et al., 2011; Kumar and Goel, 2019). Phenolic compounds are essential in the prevention of both type 1 and type 2 diabetes as they can facilitate insulin production by the pancreatic β-cells and also activate insulin receptors (Hanhineva et al., 2010). For instance, ferulic acid (FA) enhanced the activities of glucokinase and also promoted glycogenesis in mice (Jung et al., 2007). These findings imply that FA could be relevant in the treatment or prevention of type 2 diabetes. GLUT4 is an insulin-dependent transmembrane carrier protein that is often translocated from the intracellular pool to the plasma membrane to facilitate glucose uptake by muscles and adipocytes. Gallic acid (GA) has been demonstrated to have enhanced or promoted the translocation of GLUT4 to the plasma membrane (Prasad et al., 2010). Hence, it contributes to the mitigation of type 2 diabetes by enhancing the adequate uptake of glucose by cells. Phenolic compounds may also function as anti-diabetic agents by mimicking insulin. Green tea flavonoids including epicatechin, promote glucose uptake by cells by activating insulin receptors. In other words, they are insulin-mimetics (Ganugapati et al., 2011).

Smoothie products made of apricot, orange, grapes and parsley roots strongly inhibited the activities of carbohydrate digesting enzymes and this was attributed to their enrichment of the smoothies in phenolic acids and procyanidins (Tkacz et al., 2021) thus, consuming fruit and vegetable products may decrease one's risk of contracting diabetes as they contain phenolic compounds which are essential in the regulation of carbohydrates metabolism.

Gooseberry containing a total of 41 phenolic compounds reduced postprandial blood glucose (PBG) levels in diabetic mice and also strongly and effectively inhibited α-glucosidase and α-amylase at IC_{50} values of 0.013mg/mL and 0.005mg/mL, respectively (Jiang et al., 2021). Aside from that, in a study conducted to investigate the anti-oxidant and anti-diabetic effects of gamma-irradiated pumpkin seeds dried powder (GPSDP), it was reported that the GPSDP significantly reduced glucose levels in diabetic rats. Also, GPSDP reduced lipid peroxidation, ameliorated hormonal disturbances and enhanced testicular anti-oxidant status. These effects manifested by the GPSDP were as a result of its phenolic compounds content which was significantly increased by the gamma-irradiation (Azeem et al., 2021).

Currently, diabetes is treated by employing chemotherapies in conjunction with diet controls and exercise. Nonetheless, tolerance to these therapies and the efficacies of these therapies are limited and these therapies have significant negative effects (for instance sulfonylureas over time become ineffective in patients who initially responded to them) (Sakurai et al., 2008). Thus, the need for treatment alternatives in which phenolic compounds have proven to be good candidates for diabetes treatment.

Phenolic Compounds in Anti-inflammatory

A disruption in the balance between reactive species (ROS and RNS) and anti-oxidants with the former being higher causes oxidative stress which is critical in the triggering and progression of inflammation. The activation of immunological cells causes the release of proinflammatory cytokines which in turn causes the production of oxidative agents hence stimulates and amplifies inflammation. Nitric oxide synthase, cyclooxygenases (COX-1 and COX-2) via the activation of arachidonic acid whose metabolism yields prostaglandins and thromboxanes (cyclooxygenase pathway) and 5-lipoxygenase (5-LOX) which triggers the metabolism of leukotrienes via the lipoxygenase pathway contributes to the production of reactive species thus, these enzymes are critical to the occurrence and progression of inflammation (Afonso et al., 2020).

Experimental studies suggest that phytochemicals mainly phenolic compounds can contribute tremendously to the treatment of several inflammatory diseases through various mechanisms including; inhibition of intercellular adhesion molecules and the enzymes COX-2, 5-LOX and iNOS, transcription factors such as NF-κB and the inhibition of proinflammatory cytokines (Catarino et al., 2016; Debnath et al., 2013; López-Lázaro, 2009; Leyva-López et al., 2016; Azab et al., 2016). Phenolic compounds extracted from *Elsholtzia ciliate* manifested an anti-inflammatory activity by significantly reducing the expression of proinflammatory cytokines TNF-α, IL-6, and prostaglandin E2 induced by lipopolysaccharide treatment in mouse peritoneal macrophage cell culture (Pudziuvelyte et al., 2020).

The anti-inflammatory efficacy of *Thymus leptobotrys* extracts led to a very significant decrease in the edema of adult Wistar female rats than the standard drug indomethacin and the control group. This anti-inflammatory efficacy of the extracts was associated with the higher contents of the phenolic compounds gallic acid, rutin and catechin (Oubihi et al., 2020). Also, extracts of *Celtis africana* have shown strong anti-inflammatory effects by effectively decreasing edema in carrageenan-induced edema in chicks and this was a result of the presence of phenolic compounds in the extracts (Borquaye et al., 2020). Aside from that, tannin-rich sorghum extracts showed anti-inflammatory effects by inhibiting the production of NO, IL-6 and the production of intracellular ROS (Hong et al., 2020). These suggest that phenolics-containing extracts mitigate the occurrence and progression of inflammation thus, are good candidates for the treatment of inflammatory diseases.

Phenolic Compounds in Anti-microbial

Phenolic compounds especially, phenolic acids manifest anti-microbial activities. Phenolic acids possess anti-microbial potentials more than their methyl and butyl esters (Kumar and Goelb, 2019). In a study conducted to investigate the anti-microbial activities of pure flavonoids (quercetin, catechin and rutin) and non-flavonoids (gallic, vanillic, protocatechuic and caffeic acids) against *Listeria monocytogenes*, it was reported that only caffeic acid from the non-flavonoid group highly inhibited the growth of *L. monocytogenes*, but both quercetin and rutin from the flavonoid group highly inhibited *L. monocytogenes* growth (Vaquero et al., 2007). Flavonoid derivatives satisfactorily bounded and inhibited the activity of haemagglutinin-1-neuramidase (H1N1) influenza virus (Lu and Chong, 2012). Thus, drugs could be made from the derivatives of flavonoids for the treatment of these viruses. Also, maroon coat Bambara extracts demonstrated a higher inhibition against *Escherichia coli* but not *Candida albicans* and this *E. coli* inhibition efficacy of the extracts was a result of their phenolic compounds contents (Oyeyinka et al., 2021). Phenolic compounds are also excellent anti-fungal agents that can be used to prolong the shelf-life of fruits. FA efficiently protected fruits from post-harvest fruit decay-causing fungal thus, phenolic compounds especially FA can be used in post-harvest management or storage of fruits (Hernández et al., 2021).

The anti-microbial potentials of phenolic compounds can be increased by using them in conjunction with metal complexes. For instance, the cobalt-curcumin complex manifested an anti-microbial activity than curcumin alone (Hatamie et al.,2012). Furthermore, metal complexes made with curcumin has been reported to have shown an anti-microbial activity against *Pseudomonas* spp. *E. coli* and *Klebsiella pneumonia* (Subhan et al., 2014). Consequently, using phenolic compounds in the synthesizes of metal complexes yields a greater anti-microbial efficacy (Shakeri et al., 2019).

People have suffered from microorganisms-caused diseases since time immemorial (Akgul et al., 2021). Microorganisms do develop resistance for their therapeutic agents hence, limiting the success of these drugs. However, phenolic compounds which are ubiquitous, are promising anti-microbial agents.

CONCLUSION

Ensuring a good balance between reactive species (ROS and RNS) and anti-oxidants via the consumption of diets rich in phenolic compounds is crucial for the prevention of oxidative-stress related diseases such as cancer, diabetes and inflammatory diseases. Aside from that, consuming phenolics reduces one's risk of contracting microbial-borne diseases as they possess an anti-microbial potential. Consequently, phenolic compounds are potent candidates for drug development. However, further studies should be conducted to elucidate their anti-cancer, anti-diabetic, anti-inflammatory and anti-microbial mechanisms. Also,

studies should be carried to ascertain the efficacies of phenolic compounds-metal complexes in anti-cancer, anti-diabetic, anti-inflammatory and anti-microbial.

Conflict of Interest

The authors declared that there is no conflict of interest.

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