Biocatalysis and Agricultural Biotechnology 19 (2019) 101109

Contents lists available at ScienceDirect

Biocatalysis and Agricultural Biotechnology

journal homepage: www.elsevier.com/locate/bab

Diarylheptanoids as nutraceutical: A review

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ARTICLE INFO

Keywords:
Diarylheptanoids
Phenols
Nutraceuticals
Human health

ABSTRACT

Phenolic compounds are naturally occurring compounds present ubiquitously in plants. They have potential health benefits and substantiate evidence for their nutraceutical applications. Diarylheptanoids are part of the broad class of plant phenolics with structurally divergent compounds. They have been used in traditional medicines and homemade remedies to treat various ailments, as organoleptic additives in foods, and also for aesthetic purposes. With their potential therapeutic and organoleptic characteristics, diarylhepatanoids can be rightly termed as nutraceuticals. This review summarizes the wide range of pharmacological activities of diarylhepatanoids and nutraceutical formulations, with relevance to human health.

1. Introduction

Phenolic compounds have been well investigated for their disease prevention and health promoting effects based on epidemiological studies using both *in-vitro* and *in-vivo* methods (Vauzour et al., 2010; Kyselova, 2011; Działo et al., 2016). Most of them have been used in traditional medicine formulation and in pharmaceutical preparations (Asif, 2015; Tungmunnithum et al., 2018). They comprise of a wide range of compounds from simple phenols to complex polyphenols, such as phenolic acids, flavonoids, lignans and stilbenes (Lin et al., 2016; Ciulu et al., 2018). Diarylheptanoids are complex phenolic compounds having the skeletal structure of two aromatic rings conjugated with seven carbon chains (Brand et al., 2006; Amalraj et al., 2017). They are structurally diverse and have been isolated from seeds, fruits, leaves, roots, rhizomes and barks of plants of different families such as Myricaceae, Betulaceae, Zingiberaceae, Aceraceae, Leguminosae and Burseraceae (Per et al., 2002; Kawai et al., 2008; Ibrahim et al., 2017). More than 400 diarylheptanoids have been identified till now and most compounds occur in *Zingiber*, *Betula* and *Alnus* species (Vidaković et al., 2017; Alberti et al., 2018). These species exhibit characteristic aroma, and also act as colouring agents. Mostly, *Zingiber* and *Curcuma* rhizomes have been used as seasoning spices and as ingredients in folk medicines and traditional Asian medicines (Kunnumakkara et al., 2009). Organoleptic characteristics are attributed to the presence of diarylheptanoids. Singldinger et al. (2017) identified asadanin, a cyclic diarylhepatanoids responsible for the bitter off-taste in *Corylus avellana*.

2. Diarylheptanoids and dietary supplements

Nutraceuticals are bioactive compounds or extracts with scientifically evident health benefits (Cencic and Chingwaru, 2010; El-Sohaimy, 2012; Nasri et al., 2014). A dietary supplements, are available in the form of tablets, capsules or syrups targeting disease prevention and treatment (Caleja et al., 2017; Dutta et al., 2019). Epidemiological studies show that dietary supplementation of nutraceuticals such as catechins, linolenic acid, anthocyanin, lycopene, resveratrol and saponin glycosides can decrease the incidence of diseases (Cencic and Chingwaru, 2010; Aschemann-Witzel and Grunert, 2015; Ruchi, 2017). Studies have shown that nutraceuticals have the property to inhibit prostate cancer growth (Salami et al., 2013), protect against cardiovascular disease (Sosnowska et al., 2017), control cholesterol levels (Cicero et al., 2012) and andrologic disorders (Tamler and Mechanick, 2007), maintain gastrointestinal health (Romano et al., 2012) and retard degenerative disorders (Pasrija et al., 2015). Diarylheptanoids, also known as dipheylheptanoids, fall under the class of plant secondary metabolites derived from various plant sources (Table 1). It constitutes two phenolic aromatic rings linked by a linear seven-carbon chains. It can be either open chain or macrocyclic diarylheptanoids (Fig. 1) (Keserü and Nógrádi, 1995). Studies have also shown the health benefits of diarylheptanoids. Among nutraceuticals, curcumin is an important diarylheptanoid compound, studied extensively for its role in protection against many diseases (Kunnumakkara et al., 2017). Extracts of *Alpinia officinarum* contain diarylheptanoids, and are prepared as a health supplement capsule (Dong et al., 2015). Diarylheptanoids isolated from *Alnus glutinosa* have shown to protect non-cancerous dividing cells during cancer treatment (Dinić et al., 2015).

DOI of original article: https://doi.org/10.1016/j.bcab.2019.101126
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https://doi.org/10.1016/j.bcab.2019.101109
Received 15 November 2018; Received in revised form 19 March 2019; Accepted 21 March 2019
Available online 26 March 2019
1878-8181/

Table 1
Major plant sources of diarylheptanoids (Source: Lv and She, 2012).

Compounds	Resource
(−)-centrolobol	*Centrolobium robustum*
(+)-centrolobol	*Centrolobium tomentosum, Centrolobium paraense*
Diospongin C	*Dioscorea spongiosa*
Betulaplatoside Ia	*Betula platyphylla*
Betulaplatoside Ib	
(3S)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptan-3-ol	*Curcuma kwangsiensis*
(3R)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptan-3-ol	
(3S)-3-acetoxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptanes	
(3R)-3-acetoxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptanes	
(3S)-1,7-bis(4-hydroxyphenyl)-(6E)-6-hepten-3-ol	
(3R)-1-(3,4-dihydroxyphenyl)-7-phenyl-(6E)-6-hepten-3-ol	
1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one	*Curcuma longa*
1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3-one	
1,7-bis(4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3-one	
1,5-dihydroxy-1,7-bis(4-hydroxyphenyl)-4,6-heptadiene-3-one	
Dihydrodemethoxycurcumin	
1-hydroxy-1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-6-hepten-3,5-dione	
3,5-diacetoxy-1-(3,4-dihydroxyphenyl)-7-(3,4-dihydroxy-5-methoxyphenyl)heptanes	*Zingiber officinale*
3,5-diacetoxy-1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane	
3,5-diacetoxy-7-(3,4-dihydroxy-5-methoxyphenyl)-1-(4-hydroxy-3,5-dimethoxyphenyl)heptanes	
(3R,5S)-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)heptanes	*Zingiber ottensii*
Cassumunin A, B, C	*Zingiber cassumunar*
Juglanol A 5-O-β-D-xylopyranoside	*Juglans mandshurica*
1-(4″-methoxyphenyl)-7-(4′-hydroxyphenyl)-(E)-hept-2-ene	*Pleuranhodium racemigerum*
Oregonoside A, B	*Alnus rubra*
Epihirsutanonol	*Alnus japonica*
1,7-diphenyl-3,5-heptanedione	*Alpinia conchigera*
Katsumain A, B	*Alpinia katsumadai*
Letestuianin C	*Aframomum letestuianum*
Mistletonone	*Viscum coloratum*
2,3,7-trihydroxy-5-(3,4-dihydroxy-E-styryl)-6,7,8,9-tetrahydro-5H-benzocycloheptene	*Amomum subulatum*
16-methoxy acerogenin B 9-O-β-D-apiofuranosyl-6)-β-D-glucopyranoside	*Myrica rubra*
Myricanol 5-O-β-D-glycopyranosyl-(1–3)-β-D-glucopyranoside	
Nanaone	*Myrica nana*
11-oxo-3,8,9,17-tetrahydroxy-[7,0]-metacyclophane	*Corylus sieboldiana*
11-oxo-3,12,17-trihydroxy-9-ene-[7,0]-metacyclophane	

Winuthayanon et al. (2009) showed the estrogenic activity of diarylheptanoids isolated from *C. comosa* and its role in postmenopausal hormone therapy. Cassumunarin gives excellent anti-oxidant properties (Jitoe et al., 1994), Cassumunins A, B and C isolated from *Zingiber cassumunar* showed stronger antioxidant activities than that of curcumin (Masuda and Jitoe, 1994), and studies have shown the therapeutic benefits of gingerenones (Suk et al., 2017) and platyphylloside (Karri et al., 2019) in treating obesity (see Tables 2 and 3).

3. Pharmacological activities of diarylheptanoid

Diarylheptanoid compounds possess numerous therapeutic benefits, including anti-inflammatory, anti-ulcer, anti-cathartic, anti-emetic, diuretic, choleretic, hepato-protective, cholesterol level lowering, antibacterial, anti-fungal, analeptic and anti-diabetic activities. These are discussed below:

3.1. Anti-inflammatory activity

Diarylheptanoids exhibit significant anti-inflammatory properties. Hirsutenone isolated from the bark of *A. japonica* could suppress early T-cell activation; thereby, inhibiting the degranulation of mast cells, making it a potential candidate for treating atopic dermatitis (Jeong et al., 2010). Cyclic diarylheptanoid, acerogenin M isolated from the methanol extract of *Acer nikoense* stem bark (Akihisa et al., 2006), oregonin, a diarylheptanoid derivative isolated from *Alnus formosana* (Lee et al., 2005) and cassumunarins A, B, and C from *Z. cassumunar* inhibit edema formation, exhibiting strong anti-inflammatory activity than curcumin (Masuda et al., 1995); diarylheptanoid, 7-(4′-hydroxy-3′-methoxyphenyl)-1-phenylhept-4-en-3-one from *A. officinarum* (Yadav et al., 2003) and cyclic diarylheptanoids isolated from the stem bark of *A. nikoense* such as acerosides B1 and B2, and aceroketosides inhibit the release of β-hexosaminidase (Morikawa et al., 2003). Diarylheptanoids isolated from bark of *A. hirsuta*, especially oregonin and hirsutanonol showed high anti-inflammatory activity by inhibiting the cyclooxygenase-2 expression (Lee et al., 2000). Similarly diarylheptanoid glycosides such as myricanol and myricanone isolated from *M. rubra* can inhibit the release of β-hexosaminidase from RBL-2H3 cells (Masuda et al., 2002). Blepharocalyxins A and B from *Alpinia blepharocalyx* exhibit inhibitory effects on nitric oxide production in endotoxin-activated murine macrophages (Kadota et al., 1996).

3.2. Anti-oxidant activity

Diarylheptanoids acts as potent antioxidants. Studies have reported the free oxygen radicals scavenging activity of curcumin (Unnikrishnan and Rao, 1995; Jayaprakasha et al., 2006; Ak and Gülçin, 2008). Mistletonone exhibited scavenging capability both on hydroxyl radicals and superoxide anion radicals as compared with standard (−)-epigallocatechin gallate (Yao et al., 2007). Cassumunin A, B, C and cassumunarin A, B, C isolated from *Zingiber cassumunar* are also potent antioxidants showing stronger or equal antioxidant activity as that of curcumin (Nagano et al., 1997; Masuda et al., 1995). Diarylheptanoids isolated from *Z. officinale* especially 5-[4-hydroxy-6-(4-hydroxyphenethyl)tetrahydro-2H-pyran-2-yl]-3- methoxybenzene-1,2-diol, 5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl) heptan-3-one and 1,5-epoxy-3-hydroxy-1- (4,5-dihydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl) heptanes are capable of scavenging superoxide anion radicals and inhibiting the formation of lipid peroxides in liver microsomes (Tao et al., 2008).

Table 2
Diarylheptanoid rich plant species used in traditional medicines in different countries.

Taxon	Plant part used	Purpose/target	Country/region	References
Alpinia officinarum	Rhizomes	Stomach ache and cold	China	Basri et al. (2017)
Alpinia galangal; Alpinia oxyphylla; Alpinia conchigera		Joint pain, cold and gastrointestinal disorder	Vietnam	Hanh et al. (2014)
C. longa		Gastric disorders, inflammation	India, china and South Asian countries	Prasad and Aggarwal (2011)
Tacca chantrieri		Gastric ulcers, enteritis and hepatitis	China	Yokosuka et al. (2002)
Z. officinale		Headaches, nausea, rheumatism and cold	India, China	Mishra et al. (2012)
Alpinia katsumadai	Seeds	Emesis and gastric disorders	China	Lee et al. (2003)
Alnus japonica	Bark	Cancer and hepatitis	Korea	Sati et al. (2011); Kim et al. (2004)
Alnus nepalensis		Dysentery, stomach ache, and diarrhea	India	Changkija (1999)
Alnus glutinosa		Mouth, throat inflammation and skin diseases	Britain, Western Asia, North Africa, European countries	Sati et al. (2011)
Alnus glutinosa		Swelling, inflammation, and rheumatism	India	Sati et al. (2011)
Alnus hirsuta		Fever, hemorrhage, alcoholism, and diarrhea	Korea and China	Sati et al. (2011)
Myrica esculenta		Asthma and bronchitis	India	Patel et al. (2010)
Garuga pinnata		Corneal opacity and also pulmonary infections	India	Changkija (1999)
M. rubra		Astringent, antidote, and diarrhea	Japan	Akazawa et al. (2010)
Garuga pinnata	Leaf	Asthma	India	Shirwalkar et al. (2006)
A. nepalensis		Dysentery, stomach ache, and diarrhea	India	Changkija (1999)
Acer nikoense		Hepatic disorders	Japan	Omar (2013)

3.3. Cytotoxicity and anti-carcinogenic activity

Diarylheptanoids also shows cytotoxicity and anti-cancer effects. 7-(4″-hydroxy-3″-methoxyphenyl)-1-phenyl-4E-hepten-3-one and (5R)-5-methoxy-7-(4″-hydroxy-3″ methoxyphenyl)-1-phenyl-3-heptanone isolated from *A. officinarum* were proven to have potent cytotoxicity (Tabata et al., 2009). Diarylheptanoid 1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)-4E-en-3-heptanone caused cytotoxic effect in SH-SY5Y cells by arresting the cell cycle and inducing apoptosis (Tian et al., 2009). (3S)-1,7-bis(4-hydroxyphenyl)-(6E)- 6-hepten-3-ol, centrolobol and (3S)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)-(6E)-6-hepten-3-ol isolated from rhizomes of *Curcuma elata* showed cytotoxic activity against NCI−H187 cell lines (Chokchaisiri et al., 2014). Diarylheptanoids isolated from the sea grass *Cymodocea nodosa* exhibited cytotoxic activity. Cymodienol exhibited stronger effect; whereas, cymodiene showed moderate activity (Kontiza et al., 2005). Rubanol from *M. rubra* showed cytotoxicity against Lun-06, Neu-04, and Bre-04 cell lines (Wang and Liu, 2008). Myricanone, a cyclic diarylheptanoid, showed anti-cancer effects on cancer cell lines HeLa and PC3 (Paul et al., 2013). Epicalyxin F and calyxin I isolated from ethanol extracts of *A. blepharocalyx* seeds exhibited potent anti-proliferative activity against human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma cells (Gewali et al., 1999; Ali et al., 2001). Blepharocalyxins D, E isolated from the ethanol extract of *A. blepharocalyx* seeds exhibited significant anti-proliferative activity against murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells, with ED_{50} values of 3.61 and 9.02 μM, respectively (Tezuka et al., 2000). Methanolic extract of dried fruits of *A. oxyphylla* showed potential chemo-preventive and anti-tumorigenic activities (Lee et al., 1998). Diarylheptanoid compounds isolated from the rhizomes of *T. chantrieri* exhibited considerable cytotoxic activities against HSC-2 human oral squamous carcinoma cells than against normal human gingival fibroblasts. Other studies confirmed curcumin as a potent anticarcinogenic compound (Surh et al., 2001; Shao et al., 2002; Park et al., 2013; Vallianou et al., 2015).

3.4. Anti-coagulant activity

Curcumin could restrict collagen and adrenaline-induced platelet aggregation *in vitro* as well as *in vivo* in rat thoracic aorta (Srivastava et al., 1986). Bisdemethoxycurcumin, a derivate of curcumin, inhibited the thrombin and activated factor X activity, helping to prolong the thromboplastin time and prothrombin time effect. These are preferred to patients prone to vascular thrombosis, requiring anti-coagulant therapy (Kim et al., 2012). 1, 7-bis (4-hydroxyphenyl)-3- hydroxy-1,3-heptadien-5-one isolated from *A. blepharocalyx* showed antiplatelet activity (Doug et al., 1998). Keihanian et al. (2018) reported anti-coagulant activities of curcumin and its role in treatment of cardiovascular diseases.

3.5. Anti-adipogenic effect

Platyphylloside isolated from *Betula platyphylla* showed potent *anti*-adipogenic activities by inhibiting adipocyte differentiation in 3T3-L1 cells (Lee and Sung, 2016). Diarylheptanoids isolated from *A. hirsuta* leaves, particularly platyphyllonol-5-O-b-D-xylopyranoside showed high adipocyte differentiation (Lee et al., 2013). Methanol extract of *A. japonica* fruits, especially, 4-hydroxy-alnus-3,5-dione, exhibited the significant *anti*-adipogenic effects (Sung and Lee, 2015). Zhang et al. (2018) extracted five different diarylheptanoids, such as *trans*-(4R,5S)-epoxy-1,7-diphenyl3-heptanone, 7-(4″-hydroxy-3″-methoxyphenyl)-1-phenylhepta-4E, 6E-dien-3-one and 5-hydroxy-1,7-diphenyl-3-heptanone, 1,7-diphenyl-4E-en3-heptanone and 5-methoxy-1,7-diphenyl-3-heptanone from the aqueous extract of *A. officinarum*; all these compounds exhibited significant differentiation-promoting activity in 3T3-L1 preadipocytes.

3.6. Anti-microbial activity

Diarylheptanoids have also been investigated for anti-bacterial, anti-fungal, anti-viral activities.

a) Anti-bacterial activity.

Diarylheptanoids isolated from *A. officinarum* especially 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone, showed *anti-Helicobacter pylori* activity (Lee et al., 2009). Curcumin can inhibit the growth of several bacteria species like *Streptococcus*, *Staphylococcus* and *Lactobacillus* (Bhavani-Shankar and Sreenivasamurthy, 1979). It can also prevent growth of *Helicobacter pylori, in vitro* (Mahady et al., 2002). Diarylheptanoids such as gingerenones A, B and C as well as iso-gingerenone isolated from *Zingiber officinarum,* show moderate anti-fungal activity (Endo et al., 1990). Cyclic diarylheptanoids garuganin I isolated from *Garuga pinnata* and *G. gamblei* exhibit anti-bacterial activity (Keserü and Nógrádi, 1993), Another diarylheptanoid, 9′-Des-methylgaruganin I, isolated from *G. pinnata* showed moderate anti-microbial activity against a wide range of gram-positive and gram-negative bacteria and fungi (Khatun et al., 2013).

b) Anti-fungal activity.

Studies have shown that ether and chloroform extracts, and the oil of *C. longa* have antifungal effects (Banerjee and Nigam, 1978); particularly, curcumin has anti-fungal effects (Wuthi-Udomler et al., 2000). Turmeric oil is found to be active against *Aspergillus flavus*, *Aspergillus parasiticus*, *Fusarium moniliforme* and *Penicillium digitatum* (Jayaprakasha et al., 2001).

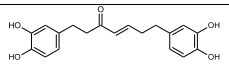
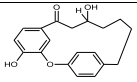
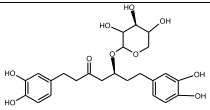
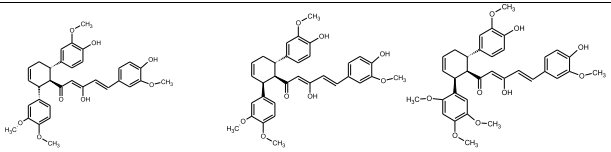
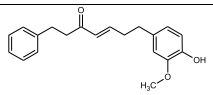
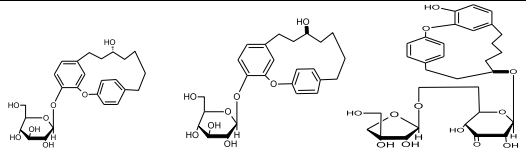
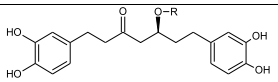
c) Anti-viral activity.

Hirsutenone exhibits strong papain-like protease inhibitory activity in suppressing the replication of the severe acute respiratory syndrome coronavirus (SARS-CoV). It can act as a potential drug target for the treatment of SARS. (Park et al., 2012). Curcumin inhibits epstein-barr virus key activator, Bam H fragment z left frame 1 (BZLF1) protein transcription in Raji DR-LUC cells (Hergenhahn et al., 2002). It also shows *anti*-HIV (human immunodeficiency virus) activity by inhibiting the HIV-1 integrase needed for viral replication (Mazumdar et al., 1995; De Clercq, 2000).

3.7. Anti-parasitic activity

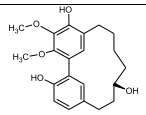
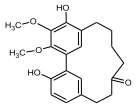
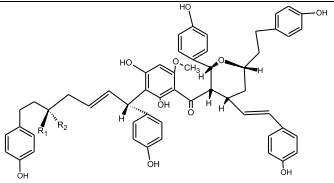
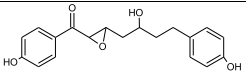
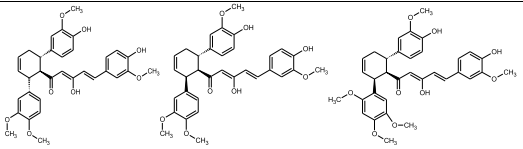
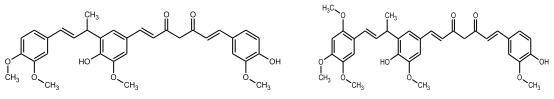
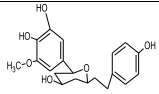
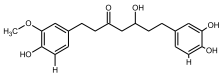
Diarylheptanoids glycosides isolated from the ethyl acetate extract of *Pyrostria major* leaf show moderate *anti*-plasmodial activities; particularly (3S,5S)-3,5-dihydroxy1-(3-hydroxy-4-methoxyphenyl)-7-(4-methoxyphenyl) heptyl 3-O-β-D-glucopyranoside shows potential anti-leishmanial activity (Beniddir et al., 2012). Studies confirm that curcumin has anti-leishmanial (Koide et al., 2002) and anti-*Plasmodium falciparum* activity (Rasmussen et al., 2000). Further, studies have shown that diarylheptanoid structure related to curcumin show anti-leishmanial activity against *Leishmania* species such as *L. amazonensis*,

Table 3
Pharmacological profile of diarylheptanoids.

Biological Activities	Compound	References
Anti-inflammatory activity	 Hirsutenone	Jeong et al., 2010
	 Acerogenin M	Akihisa et al., 2006
	 Oregonin	Lee et al., 2005
	 Cassumunarins A Cassumunarins B Cassumunarins C	Masuda et al., 1995
	 7-(4'-hydroxy-3'-methoxyphenyl)-1-phenylhept-4-en-3-one	Yadav et al., 2003
	 Acerosides B1 Acerosides B2 Aceroketoside	Morikawa et al., 2003
	 Oregonin - R = D-xylose ; Hirsutanonol – R = H	Lee et al., 2000

(*continued on next page*)

Table 3 (*continued*)

	 Myricanol  Myricanone	Masuda et al., 2002
	 Blepharocalyxins A R_1 = H; R_2 = OH Blepharocalyxins B R_1 = OH; R_2 = H	Kadota et al., 1996
Anti-oxidant activity	 Mistletonone	Yao et al., 2007
	 Cassumunarin A Cassumunarin B Cassumunarin C	Masuda et al., 1995
	 Cassumunin A Cassumunin B	Nagano et al., 1997
	 5-[4-hydroxy-6-(4-hydroxyphenethyl)tetrahydro-2H-pyran-2-yl]-3-methoxybenzene-1,2-diol  5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)heptan-3-one	Tao et al., 2008

(*continued on next page*)

Table 3 (*continued*)

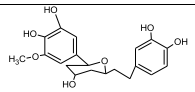
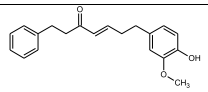
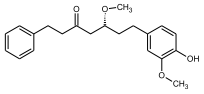
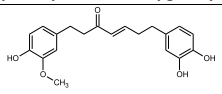
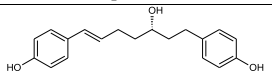
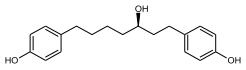
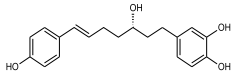
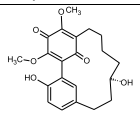
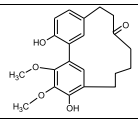
	 1,5-epoxy-3-hydroxy-1-(4,5-dihydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)heptanes	
Cytotoxicity and anti-carcinogenic activity	 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-4E-hepten-3-one  (5R)-5-methoxy-7-(4"-hydroxy-3" methoxyphenyl)-1-phenyl-3-heptanone	Tabata et al., 2009
	 1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)-4E-en-3-heptanone	Tian et al., 2009
	 (3S)-1,7-bis(4-hydroxyphenyl)-(6E)- 6-hepten-3-ol  Centrolobol  (3S)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)-(6E)-6-hepten-3-ol	Chokchaisiri et al., 2014
	 Cymodienol	Kontiza et al., 2005
	 Rubanol	Wang and Liu, 2008
		Paul et al., 2013

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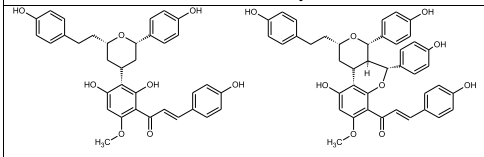
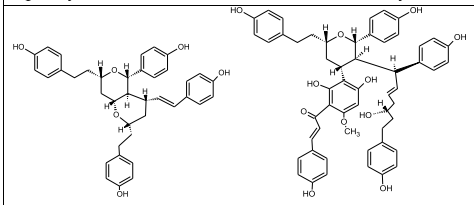
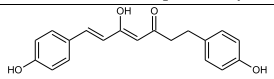
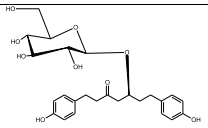
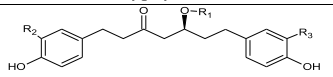
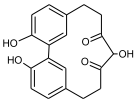
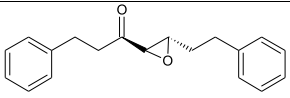
Table 3 (*continued*)

	Myricanone	
	 Epicalyxin F Calyxin	Gewali et al., 1999; Ali et al., 2001
	 Blepharocalyxins D Blepharocalyxins E	Tezuka et al., 2001
Anti-coagulant activity	 1,7-bis (4-hydroxyphenyl)-3- hydroxy-1,3-heptadien-5-one	Doug et al., 1998
Anti-adipogenic activity	 Platyphylloside	Lee and Sung, 2016
	 Platyphyllonol-5-O-b-D-xylopyranoside R_1 = β-D –xylopyranoside; R_2 = H; R_3 = H	Lee et al., 2013
	 4-hydroxy-alnus-3,5-dione	Sung et al., 2015.
	 trans-(4R,5S)-epoxy-1,7-diphenyl3-heptanone	

(*continued on next page*)

Table 3 (*continued*)

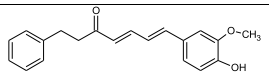
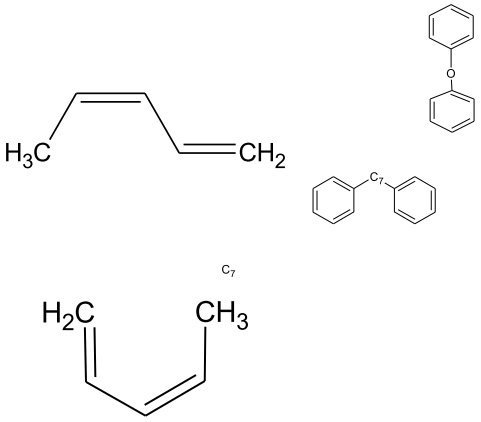
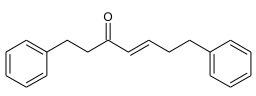
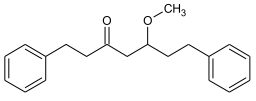
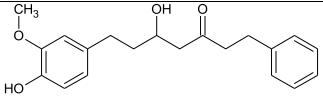
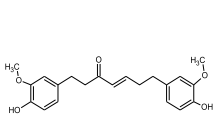
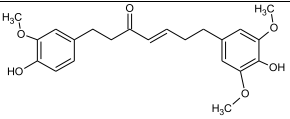
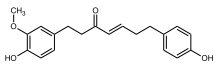
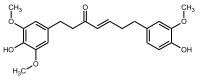
	 7-(4″-hydroxy-3″-methoxyphenyl)-1-phenylhepta-4E, 6E-dien-3-one	Zhang et al., 2017
	 5-hydroxy-1,7-diphenyl-3-heptanone  1,7-diphenyl-4E-en3-heptanone  5-methoxy-1,7-diphenyl-3-heptanone	
Anti-microbial activity	 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone	Lee et al., 2009
	 Gingerenones A  Gingereones B  Gingereones C  Isogingerenone	Endo et al., 1990

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Table 3 (*continued*)

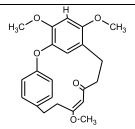
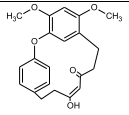
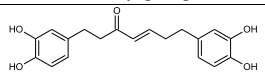
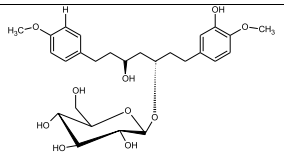
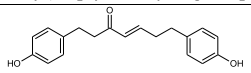
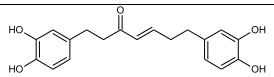
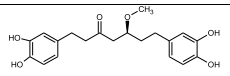
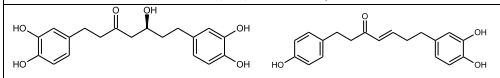
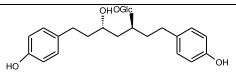
	 Garuganin I	Keserü and Nógrádi, 1993
	 9′-Desmethylgaruganin I	Khatun et al., 2013
	 Hirsutenone	Park et al., 2012
Anti-parasitic activity	 (3S,5S)-3,5-dihydroxy1-(3-hydroxy-4-methoxyphenyl)-7-(4-methoxyphenyl)heptyl 3-O-β-d-glucopyranoside	Beniddir et al., 2010
Anti-fibrotic activiy	 1,7-bis-(4-hydroxyphenyl)-5-hepten-3-one	Lee et al., 2012
	 Dehydrohirsutanonol	Lee et al., 2011
Hepato-protective activity	 (5S)-O-methylhirsutanonol	Park et al., 2010
	 Hirsutanonol Alusenone	Tung et al., 2010
	 Betulaplatoside I a	Matsuda et al., 1998

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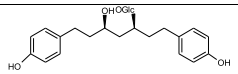
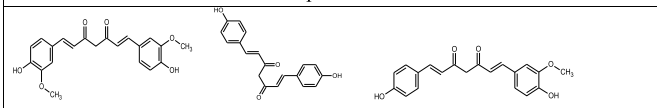
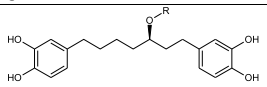
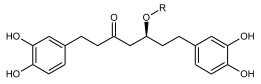
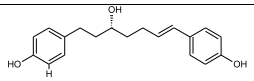
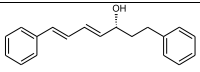
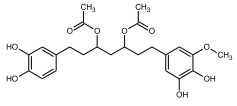
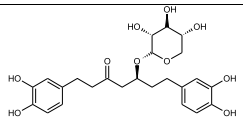
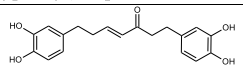
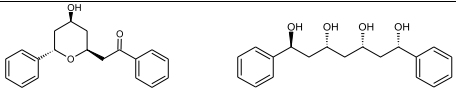
Table 3 (*continued*)

	 Betulaplatoside I b	
	 Curcumin Bisdemethoxycurcumin Demethoxycurcumin	Song et al., 2001
Melanogenesis inhibitory activity	 Acerogenin M Aceroside I	Akazawa et al., 2006
	 (5R)-l,7-bis (3,4-dihydroxyphenyl)-heptane-5-O-I~-D-glucoside R = Glc	Cho et al., 2002
	 (5R)- 1,7-bis (3,4-dihydroxyphenyl)-heptane-5-ol Hirsutanonol R – H; Oregonin – R – Xyl	
	 (3R)-1,7-bis(4-hydroxyphenyl)-(6E)-6-hepten-3-ol	Matsumoto et al., 2013
Estrogenic activity	 (3*R*) -1,7-diphenyl-(4*E*,6*E*) -4,6-heptadien-3-ol	Winuthayanon et al., 2009
	 dihydrogingerenone A dihydrogingerenone B  3,5-diacetoxy-1-(3’ ,4’ - dihydroxyl phenyl)-7-(3’’,4’’-dihydroxy-5’’-methoxyphenyl)heptanes	El-Halawany and Hattori, 2012

Anti-diabetic activity	 1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O-β-D-xylopyranoside	Hu and Wang, 2011
Anti-ulcerogenic activity	 Curcumin	Tuorkey and Karolin, 2009, Mei et al., 2009
Anti-fertility activity		Liao et al., 2001
Antio-steoporotic activity	 Diospongin B Diospongin C	Yin et al., 2004

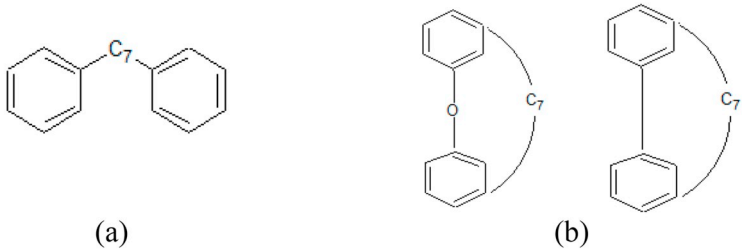


Fig. 1. Structure of diarylheptanoids (a) open (b) macrocyclic.

L. braziliensis and *L. chagasi* through both *in vitro* and *in vivo* methods (Alves et al., 2003).

3.8. Anti-fibrotic effect

Diarylheptanoids constituents of *B. platyphylla* showed anti-fibrotic effect. Particularly, the n-butanol fraction containing 1,7-bis-(4-hydroxyphenyl)-5-hepten-3-one significantly decreased the collagen content and increased the caspase-3/7 activity (Lee et al., 2012). In another study, curcumin could suppress bleomycin-induced pulmonary fibrosis in rats (Srivastava et al., 1985; Punithavathi et al., 2000). Dehydrohirsutanonol, an active constituent isolated from *A. firma* exhibits anti-fibrotic activity and can be recommended as a therapeutic agent for liver fibrosis (Lee et al., 2011). Crude fractions of *Curcuma* species such as *C. aromatica, C. longa, C. caesia, C. amada and C. zedoria* with diarylheptanoids have been dialyzed and investigated for their coagulation cascade with respect to pro-coagulant activity. Results confirmed reducing clotting time, confirming its fibrino-genolytic acitivty (Shivalingu et al., 2015).

3.9. Hepatoprotective activity

Diarylheptanoids, such as epihirsutanonol and alusenone isolated from *A. japonica* show hepato-protective properties (Tung et al., 2010). Ethyl acetate extracts of *A. hirsuta* containing diarylheptanoid glycoside, (5S)−O-methylhirsutanonol showed strong hepatoprotective effects (Park et al., 2010). Betulaplatosides Ia and Ib isolated from methanolic extract of *B. platyphylla* bark showed concentration dependent hepatoprotective activity (Matsuda et al., 1998). Curcumin, bisdemethoxycurcumin and demethoxycurcumin exhibit strong anti-hepatotoxic activity on tacrine induced cytoxicity in human liver derived Hep G2 cells (Song et al., 2001).

3.10. Melanogenesis inhibitory

Cyclic and acyclic diarylheptanoids aceroside I and acerogenin M isolated from the ethyl acetate fraction of the methanol extract of *A. nikoense* showed melanogenesis inhibitory effects with less toxicity to the cells (Akazawa et al., 2006). Methanol extracts of *M. rubra* bark exhibit potent inhibitory activity with reduction of melanin content (Akazawa et al., 2010). Diarylheptanoids isolated from *A. hirsuta* such as (5R)-l,7-bis (3,4-dihydroxyphenyl)-heptane-5-O-I ~ -D-glucoside, (5R)- 1,7-bis (3,4-dihydroxyphenyl)-heptane-5-ol, oregonin and hirsutanonol showed melanogenesis inhibitory activity (Cho et al., 2002). Methanolic extract from the dried rhizomes of *Curcuma comosa* showed melanogenesis effect, particularly, (3R)-1,7-bis(4-hydroxyphenyl)-(6E)-6-hepten-3-ol exhibits strong inhibitory effects (Matsumoto et al., 2013).

3.11. Estrogenic activity

Diarylheptanoids isolated from *Aframomum melegueta* showed anti-estrogenic activity as compared through *in silico* approaches. Dihydrogingerenone A, dihydrogingerenone B, 3,5-diacetoxy-1-(3',4' -dihydroxyl phenyl)-7-(3″,4″-dihydroxy-5″-methoxyphenyl) heptanes are examples (El-Halawany and Hattori, 2012). (3*R*) −1,7-diphenyl-(4*E*,6*E*) −4,6-heptadien-3-ol, isolated from *C. comosa* showed estrogenic activity, both *in vitro* and *in vivo,* by inducing estradiol-regulated endogenous genes in MCF-7 cells (Winuthayanon et al., 2009).

3.12. Anti-diabetic effects

Diarylheptanoid 1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O-β-D-xylopyranoside isolated from the stem bark of *A. hirsuta* increases the glucose uptake in human hepatocarcinoma HepG2 cells and thereby improves glucose metabolism (Hu and Wang, 2011). Curcumin decreases advanced glycation end-product induced complications in diabetes mellitus (Sajithlal et al., 1998). Studies also prove that it decreases blood sugar level in alloxan-induced diabetes in rat (Arun and Nalini, 2002). It can also prevent galactose-induced cataract formation at very low doses (Suryanarayana et al., 2003).

3.13. Other bioactivities of diarylheptanoid

Diarylheptanoids also possess various other potential pharmacological activities. Anti-ulcerogenic studies have shown gastroprotective and antiulcerogenic effect of curcumin by induction of angiogenesis in the granular tissue of ulcers. It has excellent therapeutic potential in restoration of *Helibacter pylori* induced gastric damage (Tuorkey and Karolin, 2009; Mei et al., 2009). Curcumin inhibits 5 alpha reductase activity, normally involved in the conversion of testosterone to 5*a*-dihydrotestosterone (Liao et al., 2001). It affects the mobility of human spermatozoa and its function *in vitro* and *in vivo* fertility (Naz and Lough, 2014). Studies have demonstrated the potential of curcumin for the development of a novel intravaginal contraceptive (Zhang et al., 2017). Diarylheptanoids isolated from *D. spongiosa* such as diospongin B and C are found to exhibit anti-osteoporotic activity by inhibiting the release of ^{45}Ca on the resorption of bone tissues, the same was compared with standard drug elcitonin (Yin et al., 2004a). The aqueous extract of *D. spongiosa* exhibits significant induction of osteoblast proliferation, also inhibiting osteoclast formation against less cytotoxicity in osteoblast and bone marrow cells (Yin et al., 2004b).

4. Conclusion

There is an increasing awareness and expectancy for safe and healthy foods among public, and this has been the driving force for the incorporation of bioactive compounds in food matrices. Diarylheptanoids have a wide spectrum of health-promoting properties and are also an indispensable component in a variety of pharmaceutical, medicinal and cosmetic applications. They are found to be a key bioactive ingredient in traditional and folk medicines formulation for treating various diseases. They can be used as alternative sources for therapeutics/nutraceuticals. Further research is needed to best utilize diarylheptanoids in diet, with the focus to promote human health and wellness.

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