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Diarylheptanoids as nutraceutical: A review

G. Ganapathy, R. Preethi, J.A. Moses, C. Anandharamakrishnan*
Computational modeling and Nanoscale Processing Unit, Indian Institute of Food Processing Technology, Thanjavur 613005, India

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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, diarylheptanoids can be rightly termed as nutraceuticals. This review summarizes the wide range of pharmacological activities of diarylheptanoids 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; Dziabo 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; Ciuluet 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 (Kunnammakara et al., 2009). Organoleptic characteristics are attributed to the presence of diarylheptanoids. Singldinger et al. (2017) identified asadanin, a cyclic diarylheptanoid 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 Gruner, 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 (Ciceri et al., 2012) and andrologic disorders (Tamler and Mechanick, 2007), maintain gastrointestinal health (Romano et al., 2012) and retard degenerative disorders (Parsiija 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 (Kunnammakara 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).
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), Cassuminins A, B and C isolated from Zingiber cassumunar showed stronger antioxidant activities than that of curcumin (Jitoe et al., 1994), Cassuminins A, B and C isolated from Zingiber cassumunar (Jitoe et al., 1995). Diarylheptanoids, 7-(4′-hydroxy-3′-methoxyphenyl)-4,6-heptadien-3-one and 1,5-epoxy-3-hydroxy-1-(4,5-dihydroxy-3-methoxyphenyl)tetrahydro-2H-pyran-2-yl-3-methoxybenzene-1,2-diol, 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., 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 oraganin 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., 2003). Blepharocalyxins A and B from Alpinia blepharocalyx exhibit inhibitory effects on nitric oxide production in endotoxin-activated murine macrophages (Kadota et al., 1996).

### 3. Pharmacological activities of diarylheptanoid

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

#### 3.1. Anti-inflammatory activity

Diarylheptanoids exhibit significant anti-inflammatory properties. Hirsutonene 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), orogenin, a diarylheptanoid derivative isolated from Alnus formosana (Lee et al., 2005) and cassumunarin 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 oraganin 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., 2003). 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 act 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). Cassuminin A, B, and Cassuminin 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-hydroxyxphenethyl)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)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).
### 3.3. Cytotoxicity and anti-carcinogenic activity

Diarylheptanoids also show 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-heptanoate 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-heptanoate 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, cetrobrolool and (3S)-1-(3,4-dihydroxyphenyl)-(6E)-6-hepten-3-ol isolated from rhizomes of *Cucumaria elata* showed cytotoxic activity against NCI-H187 cell lines (Chokhaisiri 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*<sub>50</sub> 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 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

Platyphyloside 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 platyphylosol-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-diphenyl-3-heptanone, 7-(4'-hydroxy-3'-methoxyphenyl)-1-phenylephtea-4E, 6E-dien-3-one and 5-hydroxy-1,7-diphenyl-3-heptanone, 1,7-diphenyl-4E-en-3-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′-Desmethylgaruganin I, isolated from G. pinnata showed moderate antimicrobial 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 |
| | Acergogenin M | Akihisa et al., 2006 |
| | Oregonin | Lee et al., 2005 |
| | Cassumunarins A | Masuda et al., 1995 |
| | Cassumunarins B | Yadav et al., 2003 |
| | Cassumunarins C | Morikawa et al., 2003 |
| | 7-(4′-hydroxy-3-methoxyphenyl)-1-phenylhept-4-en-3-one | Lee et al., 2000 |
| | Acerosides B1 | (continued on next page) |
| | Acerosides B2 | |
| | Aceroketoside | |
| | Oregonin - R = D-xylene; Hirsutanonel - R = H | |

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Table 3 (continued)

| Chemical Structure | Anti-oxidant activity | Reference |
|--------------------|------------------------|-----------|
| ![Myricanol](image1) ![Myricanone](image2) | Masuda et al., 2002 | |
| ![Blepharocalyxins](image3) | Kadota et al., 1996 | |
| ![Mistletonone](image4) | Yao et al., 2007 | |
| ![Cassumunarin A](image5) ![Cassumunarin B](image6) ![Cassumunarin C](image7) | Masuda et al., 1995 | |
| ![Cassumunin A](image8) ![Cassumunin B](image9) | Nagano et al., 1997 | |
| ![5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)heptan-3-one](image10) | Tao et al., 2008 | |

(continued on next page)
### Table 3 (continued)

| Compound Description | Structure | Source |
|----------------------|-----------|--------|
| 1,5-epoxy-3-hydroxy-1-(4,5-dihydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)heptanes | ![Structure](image1) | **Cytotoxicity and anti-carcinogenic activity** |
| 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-4E-hepten-3-one | ![Structure](image2) | Tabata et al., 2009 |
| (5R)-5-methoxy-7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3-heptanone | ![Structure](image3) | Tian et al., 2009 |
| 1-(4-hydroxy-3-methoxyphenyl)-7-(3,4-dihydroxyphenyl)-4E-en-3-heptanone | ![Structure](image4) | Chokchaisiri et al., 2014 |
| (3S)-1,7-bis-(4-hydroxyphenyl)-(6E)-6-hepten-3-ol | ![Structure](image5) | Centrollobol |
| (3S)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)-(6E)-6-hepten-3-ol | ![Structure](image6) | Cymodiencol |
| | ![Structure](image7) | Rubanol |
| | ![Structure](image8) | Kontiza et al., 2005 |
| | ![Structure](image9) | Wang and Liu, 2008 |
| | ![Structure](image10) | Paul et al., 2013 |

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Table 3 (continued)

| Myricanone | Gewali et al., 1999; Ali et al., 2001 |
|------------|-----------------------------------|
| Epicalyxin F |                                   |
| Calyxin     |                                   |
| Blepharocalyxins D |                     |
| Blepharocalyxins E |                     |
| 1,7-bis (4-hydroxyphenyl)-3- hydroxy-1,3-heptadien-5-one | Doug et al., 1998 |
| Platypilloside |                            |
| Platypyllonol-5-O-b-D-xylopyranoside | Lee et al., 2013 |
| $R_1 = \beta$-D-xylopyranoside; $R_2 = H; R_3 = H$ |                            |
| 4-hydroxy-alnu-3,5-dione | Sung et al., 2015 |
| trans-(4R,5S)-epoxy-1,7-diphenyl3-heptanone |               |

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Table 3 (continued)

| Anti-microbial activity | 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 |       |
|                         | 5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-heptanone | Lee et al., 2009 |
| Gingerenones A | Gingerenones B | Endo et al., 1990 |
| Gingerenones C | Isogingerenone | |

(continued on next page)
| Activity                  | Compound                                                                 | Reference        |
|--------------------------|--------------------------------------------------------------------------|------------------|
| Anti-parasitic activity  | Garuganin I                                                              | Keserü and Nógrádi, 1993 |
|                          | 9'-Desmethylgaruganin I                                                  | Khatun et al., 2013 |
|                          | Hirsutenone                                                              | Park et al., 2012 |
|                          | (3S,5S)-3,5-dihydroxy-[(3-hydroxy-4-methoxyphenyl)-7-(4-methoxyphenyl)heptyl-3-O-β-d-glucopyranoside] | Beniddir et al., 2010 |
| Anti-fibrotic activity   | 1,7-bis-(4-hydroxyphenyl)-5-hepten-3-one                                  | Lee et al., 2012  |
|                          | Dehydrohirsutanonol                                                      | Lee et al., 2011  |
| Hepatoprotective activity| (SS)-O-methyl/hirsutanonol                                               | Park et al., 2010 |
|                          | Hirsutanonol                                                             | Tung et al., 2010 |
|                          | Alusenone                                                                | Matsuda et al., 1998 |
|                          | Betula platoside 1a                                                      |                  |

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| Table 3 (continued) |
|---------------------|

| Melanogenes is inhibitory activity |
|-----------------------------------|
| Acergenin M                     |
| Acerside I                      |
| (5R)-1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-O-1--D-glucoside R = Glc |
| (5R)-1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-ol Hirsutanol R = H; Oregonin R = Xyl |
| (3R)-1,7-bis(4-hydroxyphenyl)-(6E)-6-hepten-3-ol |

| Estrogenic activity |
|---------------------|
| (3R)-1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol |
| dihydrogingererenone A |
| dihydrogingererenone B |
| 3,5-diacetoxy-1-(3'-4'· dihydroxy phenyl)-7-(3''4''-dihydroxy-5''· methoxyphenyl)heptanes |

| Anti-diabetic activity |
|------------------------|
| 1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O-β-D-xylopyranoside |

| Anti-ulcerogenic activity |
|---------------------------|
| Curcumin |

| Anti-fertility activity |
|-------------------------|
| Liao et al., 2001 |

| Antiosteoporotic activity |
|---------------------------|
| Diospongin B |
| Diospongin C |

| Sources |
|---------|
| Song et al., 2001 |
| Akazawa et al., 2006 |
| Cho et al., 2002 |
| Matsumoto et al., 2013 |
| Winuthayan on et al., 2009 |
| El-Halawany and Haitori, 2012 |
| Hu and Wang, 2011 |
| Tuorkey and Karolinn, 2009; Mei et al., 2009 |
| Yin et al., 2004 |
Diarylheptanoids of \textit{D. spongiosa} such as \textit{E. hirsuta} and \textit{A. japonica} show hepatoprotective properties (Tung et al., 2010). Ethyl acetate extracts of \textit{A. hirsuta} containing diarylheptanoid glycoside, \((5S)-O\)-methylhirsutanonol showed strong hepatoprotective effects (Park et al., 2010). Betulatosides Ia and Ib isolated from methanolic extract of \textit{B. platyphylla} bark showed concentration dependent hepatoprotective activity (Matsuda et al., 1998). Curcumin, bisdehydroxycumurin and demethoxycurcumin exhibit strong anti-hepatotoxic activity on tacrine induced cytotoxicity in human liver derived Hep G2 cells (Song et al., 2001).

\subsection*{3.9. Hepatoprotective activity}

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

\subsection*{3.10. Melanogenesis inhibitory activity}

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

\subsection*{3.11. Estrogenic activity}

Diarylheptanoids isolated from \textit{Aframomum melegueta} showed antiestrogenic activity as compared through in silico approaches. Dihydrogingereneone A, dihydrogingereneone B, 3,5-diacetoxy-1-(3’,4’-dihydroxyl phenyl)-7-(3’’,4’’-dihydroxy-5’’-methoxyphenyl) heptanes are examples (El-Halaway and Hattori, 2012). \((3R)-1,7\)-diphenyl-(4\(E\),6\(E\)) \(-4,6\)-heptadien-3-ol, isolated from \textit{C. comosa} showed estrogenic activity, both \textit{in vitro} and \textit{in vivo}, by inducing estradiol-regulated endogenous genes in MCF-7 cells (Winuthayanon et al., 2009).

\subsection*{3.12. Anti-diabetic effects}

Diarylheptanoid \((3R)-1,7\)-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-(4\(E\),6\(E\)) \(-4,6\)-heptadien-3-ol isolated from the stem bark of \textit{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).

\subsection*{3.13. Other bioactivities of diarylheptanoid}

Diarylheptanoids also possess various other potential pharmacological activities. Anti-ulcerogenic studies have shown gastroprotective and antitumorigenic effect of curcumin by induction of angiogenesis in the granular tissue of ulcers. It has excellent therapeutic potential in restoration of \textit{Helibacter pylori} induced gastric damage (Tuorkey and Karol, 2009; Mei et al., 2009). Curcumin inhibits 5 alpha reductase activity, normally involved in the conversion of testosterone to 5a-di-hydrotestosterone (Liao et al., 2001). It affects the mobility of human spermatozoa and its function in vitro and in vivo fertility (Náz 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 \textit{D. spongiosa} such as diospongin B and C are found to exhibit anti-osteoporotic activity by inhibiting the release of \textit{\(45\)Ca} on the resorption of bone tissues, the same was compared with standard drug elcitonin (Yin et al., 2004a). The aqueous extract of \textit{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).

\section*{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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