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Review

Dihydromyricetin: A review on identification and quantification methods, biological activities, chemical stability, metabolism and approaches to enhance its bioavailability

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ABSTRACT

Background: Dihydromyricetin (DMY) is an important plant flavonoid, which has received great attention due to its health-benefiting activities, including antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic and neuroprotective activities. DMY capsules have been sold in US as a nutraceutical supplement to prevent alcoholic hangovers. The major disadvantage associated with DMY is its chemical instability and poor bioavailability caused by the combined effects of its low solubility and poor membrane permeability. This limits its practical use in the food and pharmaceutical fields.

Scope and approach: The present paper gives an overview of the current methods for the identification and quantification of DMY. Furthermore, recent findings regarding the main biological properties and chemical stability of DMY, the metabolism of DMY as well as different approaches to increase DMY bioavailability in both aqueous and lipid phases are discussed.

Key findings and conclusions: Current trends on identification and quantification of DMY have been focused on spectral and chromatographic techniques. Many factors such as heat, pH, metal ions, could affect the chemical stability of DMY. Despite the diverse biological effects of DMY, DMY faces with the problem of poor bioavailability. Utilization of different delivery systems including solid dispersion, nanocapsule, microemulsion, cyclodextrin inclusion complexes, co-crystallization, phospholipid complexes, and chemical or enzymatic acylation has the potential to improve both the solubility and bioavailability. DMY digested in laboratory animals undergoes reduction, dehydroxylation, methylation, glucuronidation, and sulfation. Novel DMY delivery systems and basic pharmacokinetic studies of encapsulated DMY on higher animals and humans might be required in the future.

1. Introduction

As a class of polyphenol secondary metabolites, flavonoids are frequently found in plants and foods. They possess various bioactive effects including antioxidant, antibacterial, antiviral, anti-inflammatory, anti-cancer and neuroprotective activities, etc (Wang, Li, & Bi, 2017). Dihydromyricetin (DMY) or ampelopsin is a major bioactive flavonoid isolated from a traditional Chinese medicinal plant \textit{Ampelopsis grossedentata} (Zheng & Liu, 2006) and it is also found in various plant-based foods such as grapes and red bayberry (Gadetskaya, Tarawneh, & Zhusupova, 2015; Wu, Ma, & Li, 2015). DMY was first isolated from \textit{Ampelopsis meliaeifolia} by Kotake and Kubota in 1940, and was later reported as a major bioactive component in \textit{A. grossedentata} (Zhang, Yang, & Xiong, 2001; Kou & Chen, 2012). The content of DMY was as high as 30–40\% (w/w) in \textit{A. grossedentata} (Tian, Zhang, Yang, Yang, & Gong, 2002; Gao, Lee, Li, & Lee, 2016). Other major sources of DMY also include medical plants such as \textit{Hovenia dulcis} (Yoo, Mun, & Kim, 2006; Chaturvedula & Ruo, 2013) and \textit{Cedrus deodara} (Liang, Shen, et al., 2014).

Due to its beneficial activities, there have been extensive studies on DMY structure identification, content determination, as well as pharmacological effects (Kou & Chen, 2012; Li et al., 2017). On one hand, a number of spectral (Ignat, Volf, & Popa, 2011) and chromatographic methods (Ignat et al., 2011; Nazzk & Shahidi, 2006) have been...
developed for analysis and quantification of DMY. On the other hand, numerous research efforts have been devoted to the study of biological and pharmacological activities of DMY, such as antioxidative, anti-bacterial, anti-inflammatory, anti-cancer, anti-obesity and neuroprotective effects, etc (Kou & Chen, 2012; Li et al., 2017). Nowadays, DMY prescription is specially recommended for the treatment of various diseased conditions such as alcohol use disorders and metabolic or neuro imbalance (Li et al., 2017). Presently, DMY capsules are sold in the United States as a nutraceutical supplement to prevent alcohol hangovers (DSDL, 2016).

The major disadvantages associated with DMY use is chemical instability and poor bioavailability. DMY is soluble only in hot water and ethanol and slightly soluble in water under room temperature (0.2 mg/ml at 25 °C), which is the main cause of its poor membrane permeability (P = (1.84 ± 0.37) × 10⁻⁶ cm/s) and bioavailability (Tong et al., 2015; Wang, Tong, et al., 2016). This is a determinant factor that limited the pharmacological effects and clinical application of DMY. To improve the bioavailability of DMY, researchers have tried to use DMY in new drug delivery systems such as inclusion complexes (Liu, Ma, et al., 2012; Ruan, Yu, Fu, & Zhu, 2005; Yang, Liu, Liu, & Zhang, 2011), nano-encapsulate (Dalcin et al., 2017) or microemulsion (Solanki, Sarkar, & Dhanwani, 2012), co-crystals (Wang, Tong, et al., 2016), phospholipid complexes (Liu, Du, Jie, Chen, & Niu, 2009), and acylation (Cao et al., 2017; Guo, Zeng, Lu, & Shu, 2013; Li et al., 2015; Li, Zheng, & Ning, 2005) to provide higher solubility and bioavailability. In addition, the pharmacokinetic characteristics of DMY in animal models and human body are also available to the evaluation of their in vivo bioavailability efficacy. However, only partial information (Fan, Tong, & Dong, 2017; Xiang, Fan, & Hou, 2018; Zhang et al., 2007) is available on basic pharmacokinetic studies of DMY such as absorption, distribution, metabolism and excretion in organisms, biotransformation processes and metabolites.

The objective of this article is to give an overview of the current methods for analysis and quantification of DMY, as well as recent findings regarding the main biological properties and chemical stability of DMY. Special attention is paid to the metabolic pathways of DMY and different approaches carried out to increase DMY bioavailability in both aqueous and lipid phases.

2. Analysis, identification and quantification of DMY

The analysis, characterization and quantification of flavonoids in natural sources present a challenge for many researchers (Marston & Hostettmann, 2006). Spectral techniques and chromatographic techniques have been developed for the determination of DMY in the plants, foods and biological samples.

2.1. Spectral methods

A number of spectral methods have been developed for quantification of total flavonoids and DMY. The complexation of flavonoids with Al(III) is the principle of spectrophotometric assays used for quantification of total flavonoids (Naczk & Shahidi, 2006). Simple flavonoids normally have maximal absorption between 220 and 300 nm (Owades, Rubin, & Brenner, 1958). The maximal absorption of DMY was observed at ~290 nm. The role of its C2-C3 double bond, whose presence was responsible for the absorption bands in the ultraviolet (UV) regions (Biler, Biedermann, Valentaova, Kren, & Kubala, 2017). The UV absorption was also affected by the nature of solvent employed and the pH of the solution. High pH (above 11 for DMY) induced the formation of a long-wavelength peak arising from double and/or triple deprotonation (Biler et al., 2017). Moreover, there was a possibility of interference by UV-absorbing substances such as proteins, nucleic acids and amino acids. Another spectral method Fourier transform infrared spectroscopy (FT-IR) has been used for structural elucidation of complex flavonoids isolated from natural resources (Jeon, Chun, Choi, & Kwon, 2008; Wang, Xiong, & Perumalla, 2016). FT-IR has been applied to analyze the isolated compound DMY from the bark of Salix hultenii. In a recent paper reported by Wang, Xiong, and Perumalla (2016), FT-IR has been used for quickly distinguishing homochiral (+)-DMY from racemic (+/-)DMY extracted from A. grossedentata leaves. The physicochemical properties of the two phases were also assessed using FT-IR. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are also used for elucidating the chemical structures of flavonoids. Standard ¹H, ¹³C NMR spectra can give a wealth of chemical information for identifying flavonoids. MS analysis is based on ionizing chemical species and sorting the ions based on their mass-to-charge ratios (Ignat et al., 2011). By using ¹H and ¹³C NMR and MS, purity and steric integrity of DMY were assessed (Outrup, Schaumburg, & Madsen, 1985). Recently, the active compound was identified as 2R,3R-dihydromyricetin from pine needles of Cedrus deodara based on MS and NMR data (Liang, Wu, Qiu, Zhong, & Gao, 2014).

2.2. Chromatographic methods

The identification and quantification of specific flavonoid compounds like DMY can be performed with the following chromatographic techniques like thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), high-speed counter current chromatography (HSCCC), and high-performance counter current chromatography (HPCCC). TLC is a rapid and simple method for the qualitative analysis of flavonoids in plant extracts (Ignat Volf, & Popa, 2011). He, Peli, and Zhou (2000) determined the content of DMY in A. grossedentata by using a TLC-scanner. The implementation of a modern standardized methodology led to an increasing acceptance and recognition of DMY. HPLC is another preferred method for the identification and quantification of several flavonoids due to its simplicity and sensitivity. The HPLC conditions mainly include the use of reverse phased C18 column, a binary solvent gradient, and different detection systems such as Diode Array Detection (DAD), MS or NMR (Marston & Hostettmann, 2006). HPLC methods have been successfully applied in DMY identification and quantification in healthy food for anti-hangover and hepatoprotection (Zou, Zhou, & Sun, 2017), in the fruit-stalk extract of H. dulcis (Park, Kim, & Rohman, 2016), in Yeputaoteng (Jin, Ding, & Zhang, 2014) and in red wheat (Kohyama, Chono, & Nakagawa, 2017). HPLC was also used for analysis of DMY content extracted from A. grossedentata by different extraction methods (Li, Li, & Zhang, 2008).

Other interesting chromatographic alternatives for the analysis of flavonoid compounds include HSCCC (Du, Cai, & Xia, 2002; Gao, Ma, & Chen, 2017; Ma, Zhou, & Tong, 2017) and HPCCC (Vieira et al., 2016). HSCCC is an all-liquid chromatographic technique very suitable for preparative isolation of pure compounds (Ignat et al., 2011). Recently, HSCCC was successfully used for rapid and efficient separation of antioxidants including DMY from vine tea (A. grossedentata) (Gao et al., 2017; Ma et al., 2017). Furthermore, Purification of (+)-DMY from an extract of A. grossedentata leaves was performed using a triple-column HSCCC. With a solvent system composed of n-hexane-ethyl acetate-methanol-water (1:3:2:4, v/v) 11.3 g of (+)-DMY was obtained at a purity of over 99% (Du et al., 2002). HPCCC is based on a support-free liquid-liquid centrifugal partition chromatography, which could be applied to the fast fractionation and recovery of flavonoid from plant extract. A developed HPCCC protocol was successfully used to isolate the main flavonoids including DMY from the crude extract of Impatiens glandulifera Royles (Vieira, Winterhalter, & Jerz, 2016).

Recently, the coupling of chromatographic techniques to MS or NMR has achieved growing importance for the structural elucidation of complex flavonoid compounds in natural products and biological samples. By using a HPLC-tandem electrospray ionization mass spectrometry (ESI-MS) method, the major flavonoid extracts from A. grossedentata leaves by traditional solvent extraction and recrystallization was identified as (+)-DMY (Gao, Liu, & Ning, 2009). A newly established ultra-high performance liquid chromatography-quadrupole mass
specrometry method (UHPLC-MS) was successfully used for simultaneous quantification of 10 X. sorbifolia constituents. It was found that the wood of X. sorbifolia was rich in phenolic compounds with the contents of DMY being 6.76–7.89 mg/g (Zhang, Ma, & Ma, 2015). In a recent study, UPLC-MS was successfully used for analysis of the fruit metabolome DMY in Actinidia arguta cultivars (Li, Fang, & Qi, 2018).

Besides the natural products, there are also some reports on determining DMY in biological sample by chromatographic methods. HPLC methods have been previously reported for the determination of DMY in rat plasma after orally administrating the decoction of A. grossedentata (Zhang et al., 2007) Recently, a bioanalytical method with liquid chromatography (LC–MS/MS) has been developed and validated for the quantitation of DMY in rat plasma (Liu, Yin, & Wang, 2017; Tong et al., 2015; Wu, Ma, & Zhang, 2018; Yang, Yan, & Liu, 2019), for monitoring uptake and transport of DMY in human intestinal Caco-2 cells (Xiang et al., 2018) as well as for pharmacokinetic studies of DMY in organisms including absorption, distribution, metabolism and excretion (Fan et al., 2017). In contrast with HPLC, LC–MS/MS is more rapid, more sensitive for the biological analysis.

2.3. Application of capillary electrophoresis

Capillary electrophoresis (CE) is another alternative analytical tool for separation and quantification of flavonoids based on the electrophoretic migration of charged analytes (Marston & Hostettmann, 2006). This technique offers high separation efficiency and resolution power, short analysis time and low consumption of sample (Ignat et al., 2011). CE techniques have a great potential for identification of complex multicomponent mixture at the same time with good reproducibility and sensitivity (Naczk & Shahidi, 2006). Zou, Zhou, and Sun (2016) utilized CE for simultaneous determination of 7 components including DMY in functional food for anti-hangover and hepatoprotection. A baseline separation for all the target components within 8 min was achieved. The results shown that the method could meet the requirement for quality analysis.

3. Biological activities of DMY

DMY possesses diverse biological and pharmacological activities. Conventionally, DMY is used as antioxidant, antimicrobial, antiviral and anti-inflammatory agent. Current research has also shown its therapeutic benefits for the treatment of various chronic diseases such as cancer, diabetes, obesity, alcohol use disorders and metabolic or neuro imbalance (Kou & Chen, 2012; Li et al., 2017).

3.1. Antioxidant activity

Reactive oxygen species (ROS) including superoxide anion (O2−), hydroxyl radicals (OH) and hydrogen peroxide (H2O2) are produced in large amounts due to various reactions going inside human body. Oxidative damage induced by these free radicals can create deleterious effects on cells and tissues and may cause several biochemical problems including protein aggregation, DNA degradation, and oxidation of membrane lipids (Park, Chong, & Mi, 2016). Flavonoids are one of the most powerful scavengers of harmful free radicals (Burdas & Oleszek, 2001). DMY has been shown to be a strong antioxidant agent both in vitro and in vivo (Table 1). DMY inhibited the increase of lipid peroxidation (LPO) in a concentration dependent manner in linoleic acid system (Zhang, Ning, Yang, & Wu, 2003). Gao, Liu, and Ning (2009) observed that antioxidant activity of flavonoid-rich extracts (DMY) from A. grossedentata leaves were comparable with that of tertiary butylhydroquinone (TBHQ) in a linoleic acid system. The antioxidant activity of DMY was also confirmed in lard oil (Zhao et al., 2009), soybean oil (Ye, Wang, Duncan, Eigal, & O’Reeke, 2015), sausage (Wang, Qin, Yang, Lu, & Qin, 2017) and cooked ground beef (Ye et al., 2015). The possible reason for its high antioxidant activity was due to the free hydroxyl in the C-3 position in C-ring and o-dihydroxy system (hydroxyl in the C-3’ and 4’ position) in the B-ring, which has been shown strong effect against free radicals (Burdas & Oleszek, 2001).

The antioxidant effects of DMY were also demonstrated in various cell-type assays and animal models. DMY exhibited antioxidant activity in oleic acid-induced lipid accumulation process in L02 and HepG2 cells due to a decrease in the levels of cellular triglycerides (TG), cholesterol (TC) and malondialdehyde (MDA) and an increase of superoxide dismutase (SOD) level (Xie et al., 2016).

In the case of human umbilical vein endothelial cells (HUVECs) (Hou et al., 2015a) and MG63 cell (Wang, Jiao, Zhou, & Liu, 2016), DMY demonstrated a protective effect against H2O2-induced oxidative stress. Similarly, DMY protected mouse kidney tissues against nephrotoxicity through attenuation of cisplatin-induced oxidative stress and inflammatory stress (Wu et al., 2016). Moreover, DMY increased the total antioxidant capacity (T-AOC) and attenuated ROS generation in Ang-II induced cardiac fibroblasts neonatal Sprague-Dawley rats model (Meng et al., 2015; Song et al., 2017) and low-density lipoprotein (LDL) receptor deficient mice (Liu, Zeng, et al., 2017).

3.2. Antimicrobial and antiviral activity

Flavonoids may serve as pharmacologically acceptable antimicrobial agents (Cushnie & Lamb, 2005). Plant flavonoid DMY from A. grossedentata (Liu, Pang, Ding, & Sun, 2016) and Cedrus deodara (Zeng, He, Sun, Zhong, & Gao, 2012) displayed strong antibacterial activities against both Gram-negative and Gram-positive bacteria. Liu et al. (2016) confirmed the inhibitory effect of DMY on Gram-negative food pathogen V. parahaemolyticus. The inhibitory effect increased with the increase of DMY concentration, the minimum inhibitory concentration (MIC) of DMY against V. parahaemolyticus was observed at 0.625 mg/mL. Membrane damage was assumed to be the main antibacterial mechanism of DMY. In addition, it was observed that DMY could bind to proline dehydrogenase (PDH), a key regulatory and rate-limiting enzyme in the metabolism of proline. DMY interacted with primary amino acid residues (Glu 292, Arg 288, Tyr 285, Gly 64) located within the active hydrophobic pockets of PDH (Fig. 1a), leading to the decrease of PDH activity. The interference of normal proline metabolism by DMY was another possible reason for V. parahaemolyticus cell death (Ding, Xiao, Liu, & Pang, 2017).

DMY also exhibited antibacterial activity against Gram-positive bacteria Staphylococcus aureus (S. aureus). The MIC of DMY against S. aureus was observed at 0.125 mg/mL. DMY not only changed membrane integrity, fluidity and membrane protein conformation, but also bound to intracellular DNA through the groove-binding mode in S. aureus. DMY achieved bactericidal activity by dual effects of cell membrane damage and DNA binding (Wu, Bai, Zhong, Huang, & Gao, 2017). However, in the study of Huang, Huang, Chen, Yang, and Huang (2015), the effect of DMY on the inhibition of S. aureus PriA (SaPriA), an essential helicase for DNA replication restart, was not so significant. Furthermore, Huang (2015) investigated the inhibitory effect of DMY on dihydroxypyrimidinase, a key member in the chain of pyrimidine catabolism and metabolism of DNA base in Pseudomonas aeruginosa. DMY significantly inhibited dihydroxypyrimidinase with IC50 values of 48 μM. DMY was docked in the active site pocket of dihydroxypyrimidinase and formed a stable complex with dihydroxypyrimidinase (Fig. 1b). As a competitive inhibitor of dihydroxypyrimidinase, DMY intervention led to inhibition of bacterial growth and promotion of cell death.

Medicinal flavonoids provide an opportunity for the discovery of human immunodeficiency virus (HIV) inhibitors with lower or no toxicity and/or side effects (Narayan, Rai, & Tewtrakul, 2013). DMY was proved to be a strong HIV inhibitor during HIV-1 absorption, incubation and acute infection by Liu et al. (2004). About 70% HIV-1 CXCR-chemokine receptor 4 (CXCR4) was reduced by DMY at 1 mg/mL. The anti-HIV-1 effect of DMY was partly due to down-regulation of
CXCR4 on the surface of target cells. Grand, Garofalo and Neamati (2008) also confirmed CXCR4 was the major HIV co-receptors and promising targets for anti-HIV drugs. Moreover, Ren and Song (2005) observed that the combined use of myricitrin and DMY has shown great promising targets for anti-HIV drugs. Moreover, Ren and Song (2005) also con

Cisplatin-treated mouse model SOD, MDA, ROS, nitric oxide (NO) DMY decreased MDA level and increased SOD and NO bioactivity by DMY

Neutrotal rat cardiomyocytes ROS, MDA, SOD, CAT, glutathione (GSH) DMY decreased ROS production and attenuated H2O2-induced decrease in cell viability and apoptosis, MDA, increased SOD activity, T-AOC (total antioxidant capacity) and NO bioactivity by DMY

Ang-II induced cardiac fibroblasts ROS, MDA, SOD, CAT, gluthathione (GSH) DMY decreased ROS production and MDA level, while increased the SOD activity and T-AOC.

LDL receptor deficient mice ROS, MDA, SOD, CAT, glutathione (GSH) DMY decreased ROS production and MDA level, increased SOD, GSH and CAT levels.

3.4. Anti-cancer activity

Flavonoids from natural plants demonstrate great promise as anticancer agents (Ren, Qiao, Wang, Zhu, & Zhang, 2010; Cragg, Kingston, & Newman, 2011). Extensive researches have been conducted to the anti-cancer activities of DMY both in vitro and in vivo. These studies indicated that DMY was cytotoxic towards a number of human cancer cell lines, including carcinoma, breast, pancreatic and lung cancer cells. DMY exerted its anti-cancer effects by modulating multiple signaling pathways, including inhibition of apoptosis, anti-proliferation and metastatic inhibition, etc (Fig. 2).

3.4.1. Inhibition of apoptosis

Apoptosis is a vital process of programmed cell death involved in cell turnover. Any imbalance in this process leads to abnormal pathological conditions including cancer (Elmore, 2007). During tumorigenesis, cancer cells usually evaded apoptosis. DMY has been shown to restore and promote the apoptotic mode of cell death in many types of}

Table 1

| Study model          | Method/Assay              | Results                                                                 | References                        |
|----------------------|---------------------------|--------------------------------------------------------------------------|-----------------------------------|
| Linoleic acid system | DPPH and reducing power   | Anti-oxidative activity of flavonoid-rich extracts (DMY) comparable with that of tertiary butylhydroquinone (TBBQ) | Gao et al. (2009)                 |
| Linoeleic acid       | lipid peroxidation        | DMY greatly inhibit the increase of lipid peroxidation (LPO) values in a concentration dependent manner | Zhang et al. (2003)               |
| Lard oil             | DPPH                     | Effective in quenching DPPH with IC50 of 21.48 μM. Superior to that of TBBQ | Zhao et al. (2009)                |
| Soyizhou sausage     | Peroxide value, anisidine value, headspace volatiles | DMY was more potent than butylated hydroxylansiole (BHA) in preventing soybean oil oxidation | Ye et al. (2015)                  |
| Guizhou sausage      | Peroxide value (POV) malondialdehyde (MDA) | Inhibit the oxidation of sausage and its antioxidant effect increased with the increase of the amount of DMY. | Wang et al. (2017)                |
| Cooked ground beef   | Thio Barbatic acid reactive substances | DMY showed a high antioxidant activity and comparable with that of BHA after treatment with longer time (Day 14). | Ye et al. (2015)                  |
| LO2 and HepG2 cells  | Oleic acid-induced lipid accumulation | DMY decreased cellular triglycerides (TG), cholesterol (TC) and MDA, increased the level of superoxide dismutase (SOD) | Xie et al. (2016)                 |
| HUVECs               | SOD, MDA, ROS, nitric oxide (NO) | DMY inhibited intracellular ROS overproduction and attenuated H2O2-induced decrease in cell viability and apoptosis, | Hou et al. (2015)                 |
| MG63 cells           | H2O2-induced oxidative stress | 30 μM dose off DMY prevents hydrogen peroxide induced reduction in viability and apoptotic alterations | Wang et al. (2016)                |
| Cisplatin-treated mouse model | SOD, MDA, catalase activity (CAT) | DMY decreased MDA level and increased CAT and SOD activities in mouse kidney tissues after treatment with cisplatin | Wu et al. (2016)                  |
| Neonatal rat cardiomyocytes | ROS, MDA, SOD, T-AOC | Reduced levels of MDA, increased SOD activity, T-AOC (total antioxidant capacity) and NO bioactivity by DMY | Meng et al. (2015)                |
| Ang-II induced cardiac fibroblasts | ROS, MDA, SOD, T-AOC | DMY significantly decreased ROS production and MDA level, while increased the SOD activity and T-AOC. | Song et al. (2017)                |
| LDL receptor deficient mice | ROS, MDA, SOD, CAT, glutathione (GSH) | DMY decreased ROS production and MDA level, increased SOD, GSH and CAT levels. | Liu, Zeng, et al. (2017)          |
3.4.2. Regulation of proliferation

Apoptosis (Fan et al., 2016) markers such as Beclin1, LC3, and p62 and promoted carcinoma cells squamous cell carcinoma, DMY induced the upregulation of autophagic and human melanoma cells (Zhou et al., 2017). In head and neck squamous cell carcinoma, DMY induced the upregulation of autophagic markers such as Beclin1, LC3, and p62 and promoted carcinoma cells apoptosis (Fan et al., 2016).

3.4.2. Regulation of proliferation

Control of infinite cellular proliferation and cell-cycle abnormalities also have a potential therapeutic effect in cancer treatment (Collins, Jacks, & Pavletich, 1997). Studies have confirmed that DMY played an important role in regulating cancer cell proliferation. For instance, bladder cancer was mediated by cell cycle arrest (Perez de Castro, Montoya, & Malumbres, 2008). In hepatocellular carcinoma HepG2 and Hep3B cell lines, DMY caused cell cycle arrest in G2/M phase. However, deficiency of p53 and Chk1 failed to cause DMY-induced G2/M arrest (Huang, Hu, Zhao, Li, & Li, 2013). Moreover, DMY was found to cause cell cycle arrest in G2-M phase of osteosarcoma (Zhao et al., 2014) and in G1/S phase of human melanoma SK-MEL-28 cells (Zeng et al., 2014). Recently, Xu et al. (2017) observed that DMY produced an obvious inhibition on the proliferation of A2780 and SKOV3 ovarian cancer cell lines in a dose and time-dependent manner. The data indicated that DMY was a promising cell-cycle-interfering agent in human cancer cells.

3.4.3. Metastatic inhibition

Metastasis is a life-threatening stage involving the migration of cancerous cells from their origin to other tissues (Valastyan & Weinberg, 2011). Therefore, it is important to block the migration and invasion of tumor cells in cancer treatment. Recent studies have shown that DMY could inhibit migration and invasion of a number of human cancer cell lines. DMY inhibited the expression of CXCR4, a protein associated with prostate cancer, resulting in inhibition of invasion and migration of prostate cancer cells (Ni, Gong, Li, Abdolmaleky, & Zhou, 2012). Zhou, Zhang, Zhan, and Yong (2012) observed that DMY inhibited the invasion of human breast cancer cells in a dose-dependent manner through down-regulated expression of matrix metalloproteinase (MMP-2/-9) in both the extracellular matrix and the intracellular space. Furthermore, Zhang et al. (2014) also confirmed DMY inhibition of the expression of MMP 9, which was the key factor responsible for the migration and invasion of SK-Hep-1 cells.

3.5. Other biological activities

DMY has potential for the management of metabolic diseases, such as anti-diabetic and antiobesity. Shi et al. (2015) observed that DMY increased skeletal muscle insulin sensitivity, which was an important factor for management of insulin resistance for type II diabetes treatment. Recently, Liu, Wan, et al. (2017) found that DMY retarded hyperglycemia onset and ameliorated insulin resistance without weight gain in Zucker diabetic fatty rats. DMY also prevented the development of weight gain, hyperlipidemia, and atherosclerosis in ApoE knockout mouse model (Williams, Ensor, Gardner, Smith, & Lodder, 2015) and in LDL receptor knockout mice (Liu, Zeng, et al., 2017). Moreover, DMY has been demonstrated to increase irisin levels in serum, a new myokine correlated with body mass index (BMI), leading to amelioration of obesity diseases (Zhou et al., 2015). Furthermore, Zhou et al. (2017a) observed that DMY administration abrogated the adverse effects of palmitate, a major inducer of insulin resistance in obesity.

DMY may serve as a neuroprotectant in neurodegenerative conditions due to its antioxidant defense (Barnham, Masters, & Bush, 2004). DMY was found to attenuate brain aging in D-gal-induced rats (Kou et al., 2016). DMY also exhibited neuroprotective activity in Parkinson’s disease (PD) (Ren, Zhao, Cao, & Zhen, 2016). Moreover, DMY demonstrated the protective effects against alcohol intoxication and alcohol tolerance (Shen et al., 2012). The molecular mechanism of anti-alcohol was possibly associated with dysfunction of GABAARs in hippocampi (Li, Wu, et al., 2014).

DMY also demonstrated protective effect against a number of diseases and injuries such as blockage of melanogenesis in melanoma cells (Huang et al., 2016), alleviation of kidney injury (Wang, Wei, & Qiu, 2016) and liver injury (Chen et al., 2016; Xie et al., 2015) due to its antioxidant, anti-inflammatory and antiapoptotic, activities. A recent clinical study showed that DMY can improve glucose and lipid metabolism in patients with non-alcoholic fatty liver disease (Chen et al., 2015).

3.6. Toxic effects

Despite the diverse biological activities of plant flavonoids, one fundamental issue should be considered for the real application of plant flavonoids is its toxic effect. Since flavonoids are regular edible constituents of ordinary food or used in traditional medicine, examination of their toxic effects such as cytotoxicity, mutagenicity, genotoxicity and carcinogenicity have received increasing attention (Elliott Middleton, Kandaswami, & Theoharides, 2000). According to the published results, there is a controversy about the toxicity of plant flavonoids. On one hand, the use of plant flavonoids was regarded as non-toxic in some researches (Elliott Middleton et al., 2000; Middleton & Kandaswami, 1994). On the other hand, plant flavonoids was
considered to act as pro-oxidants (Sahu & Gray, 1996) and mutagenic agents in bacteria and mammalian test systems (Dzoyem, Hamamoto, Ngameni, Ngadiji, & Sekimizu, 2013; Skibola & Smith, 2000).

Toxicological effect of DMY was evaluated by several studies. Zhou, Hu, Zang, Qiu, and Liu (2001) assessed safety of A. grossedentata extract (Teng tea), which has high levels of DMY. Acute toxicity test, genetic toxicity tests and 90-day feeding test was conducted and found that the extract of A. grossedentata was toxicologically safe and the immunologic function was enhanced in mice. Furthermore, Zhong, Zhou, and Chen (2003) and Zhao et al. (2009) studied chronic toxicity of the total flavone of A. grossedentata. Continuous administration for a long time had no negative effect on the development and the indexes of hematology, biochemistry and pathology. They concluded that the evaluated total flavone (DMY) of A. grossedentata was toxicologically safe. Moreover, Xu, Yao, and Wu (2008) carried out acute toxicity test on DMY and found that the toxicity of DMY was very slight, and the greatest tolerance of oral gavage rats was 5.0 g/kg body weight.

4. Chemical stability

The phenol hydroxyl structure of DMY makes it unstable and undergoes many chemical changes such as oxidation, hydrolysis, ring fission and reduction, which resulted in metabolite formations (Xiang et al., 2017). Chemical stability of DMY is influenced by pH buffer, temperature, as well as the presence of metal ions such as Fe³⁺, Al³⁺, Cu²⁺. DMY was stable in weak acid solution and was unstable under the conditions of basic solution. When pH was between 1.2 and 4.6, the solution was stable. When pH was 6.0, there was some degradation (Ruan et al., 2005). Temperature also affects the stability of DMY. However, few studies have dealt with the thermal stability of DMY due to instability and further degradations under high temperature (Chaaban et al., 2017). Only Liu, Li, et al. (2012) and Liu, Ma, et al. (2012) observed 41.47% loss of DMY in water by treatment at 60 °C for 16 days. A lot still has to be discovered about the impact of heat treatment on DMY structure and the identification of the degradation products. Such findings are essential for the biological activities of DMY.

DMY can react with metal ions to form DMY-metal complexes due to its molecular structure with upper super delocalizability, integral conjugated large π bond, strong coordinated oxygen atoms and appropriate spatial configuration (Li et al., 2007; Zhang, Brodbelt, & Wang, 2005). DMY have shown better biological activity in the presence of Zn²⁺ (Wu, Zheng, & Chen, 2011), Co²⁺ (Li, Yang, Zhai, & Chen, 2014) and Ru²⁺ (Mishra, Singh, Trigun, Singh, & Pandey, 2004). There existed three potential coordination sites in the structure of DMY which can bind with metal ions: (i) between 3-hydroxy and 4-carbonyl groups in C ring (ii) between 5-hydroxy (in A ring) and 4-carbonyl (in C ring) groups, and (iii) between 3’ and 4’-hydroxy groups in B ring (Samsonowicz & Regulska, 2017). Wu et al. (2011) reported that metal ions were more likely bound to the carbonyl oxygen and 3-OH group (in C ring) of DMY, leading to its increase of biological activity.

5. Absorption, metabolism and elimination of DMY

Understanding the mechanism of DMY absorption, metabolism and elimination is essential for evaluating its bioavailability efficacy and level of drug intake (Manach, Scalbert, Morand, Remesy, & Jimenez, 2004). However, little information is available on DMY’s absorption profiles, distribution, metabolism, and excretion in animal models and in human body. In a recent study (Xiang et al., 2018), a human intestinal Caco-2 cell model was used to investigate the uptake and transport mechanism of DMY. The effect of time, concentration, pH, temperature and efflux transporters on its uptake and transport were systematically evaluated. The results showed that DMY was poorly absorbed by a passive diffusion mechanism. The uptake and transport of DMY were time and concentration dependent. Decreasing the pH from 8.0 to 6.0 markedly enhanced the DMY uptake, but didn’t significantly affect its bidirectional transport. DMY’s poor absorptions into blood and instability under the intestinal environment were also observed in a pharmacokinetic study conducted by Tong et al. (2015), which suggesting that DMY might be metabolized and eliminated in the intestinal tract. In addition, the gastrointestinal stability of DMY in vitro was investigated as well (Xiang et al., 2017). DMY was stable in simulated gastric fluids and buffer solutions (pH 1.2), but encountered a pseudo-first-order kinetic degradation in simulated intestinal fluids and buffer solutions (pH 6.8), which indicated gastrointestinal pH is an important factor that strongly influenced the stability, absorption and bioavailability of DMY (Abuhelwa, Foster, & Upton, 2016). The eflux transporters present in the human intestinal tract are assumed to be another factor that influence the processes of drug absorption and distribution (Couture, Nash, & Turgeon, 2006). Multidrug resistance protein 2 (MRP2) and breast cancer resistance protein (BCRP) were proved to be involved in the uptake and transport of DMY, which hindered absorption of DMY in the intestinal tract (Xiang et al., 2018). Previous reports revealed that the transport of flavonoids such as kaempferol (Zheng et al., 2016) and baicalein (Kalapos-Kovacs et al., 2015) was also modulated by these 2 eflux transporters in Caco-2 cells.

Recently, Fan et al. (2017) estimated tissue distribution, excretion, and metabolic profile of DMY after oral administration in rats. The results showed that unconverted DMY could be distributed rapidly in various tissues especially in the gastrointestinal tract and was able to cross the blood – brain barrier. The elimination of DMY was rapid as well, which could almost be completed within 12 h. Most of eliminated DMY (unconverted) were found in feces rather than urine. DMY metabolites were detected and identified in urine and feces. This is possibility due to the different excretion pathways. Normally, metabolites of flavonoids may follow 2 pathways of excretion, i.e., via the biliary or the urinary route. Large conjugated metabolites are more likely to be eliminated in the bile, whereas small conjugates are preferentially excreted in urine (Manach et al., 2004). The relative magnitude of urinary and biliary excretion varies from one flavonoid to another in animals (Crespy et al., 2003). Besides, metabolite structures and metabolic pathways were also identified by Fan et al. (2017). A total of eight metabolites were detected and five metabolic pathways consisting of reduction, dehydroxylation, methylation, glucuronidation, and sulfation were proposed, which was agree with the previously reported results (Zhang et al., 2007).

6. Approaches to enhance solubility and bioavailability of DMY

The biological indications mentioned above clearly indicate the potential of DMY as a natural functional modulator, but the problem with DMY use lies in its poor bioavailability and low intestine permeability. DMY is sparingly soluble in water and therefore not fully absorbed from the intestine. In fact, its aqueous solubility was only 0.2 mg/mL at 25 °C (Ruan et al., 2005), which led to an absolute bioavailability of less than 10% in rats (Levet-Traft, Gruyer, Marjanovic, & Chou, 1996; Ruan et al., 2006; Liu, Yin, Wang, & Li, 2017). A better understanding of biopharmaceutical properties of DMY would be of great help for developing strategies for bioavailability improvements. Biopharmaceutics classification system (BCS) is a useful tool for decision-making in formulation development (Amidon, Lennernas, Shah, & Crison, 1995). Based on BCS, drugs can be classified into four categories: (1) high solubility/high cell membrane permeability (class I); (2) low solubility/high cell membrane permeability (class II); and (3) high solubility/low cell membrane permeability (class III); (4) low solubility/low cell membrane permeability (class IV) (Table 2) (Kawabata, Wada, Nakatani, Yamada, & Onoue, 2011). Currently, only 4.5% of new drug candidates have both high solubility and permeability, however, an estimated 36% of marketed drugs, and nearly 90% of drugs in the developmental pipeline, are poorly water soluble (classes II and IV) (Lipp, 2013). DMY belongs to BCS class IV,
which requires the design of different formulations (Fig. 3) to increasing its aqueous and lipid solubility and bioavailability. Each formulation strategy has its own features (Table 3) and is still at an early investigational stage.

6.1. Enhanced aqueous solubility

6.1.1. Nanoparticulate systems

The decrease in the particle size leads to an increase in the saturation solubility, an enlarged surface area and wettability and a higher dissolution velocity (Vasconcelos, Sarmento, & Costa, 2007). Solid dispersion is an effective strategy to improve the bioavailability of poorly water soluble drugs (Fig. 3a). Hydrophilic polymers polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) were used as polymeric carriers to form solid dispersions by Ruan et al. (2005) to increase DMY solubility and dissolution rate. DMY concentration in water increased as a function of PEG and PVP concentration at 25 °C and 37 °C. The improvement of the solubility might be attributed to improved wettability and dispersibility of DMY by forming intermolecular hydrogen bonding between DMY and PVP or PEG. DMY was dissolved or suspended in the carrier (PVP or PEG), resulting in a really true solution (Leuner & Dressman, 2000). Solid dispersions, although effective for improving the biopharmaceutical performance of poorly soluble compounds, are faced with the problems of physical instability, recrystallization tendency and poor scale-up (Vasconcelos et al., 2007). Nanoencapsulation allows a sustained release of encapsulated drugs maintaining plasma concentrations at therapeutic levels during certain periods of time, and is very important to control drug release (Frank, Contrie, Beck, Pohlmann, & Gutierrez, 2015; Mora-Huertas, Fessi, & Eliaissari, 2010). Nanocapsules are polymeric nanoparticles composed of an oily core surrounded by a polymeric wall stabilized by surfactants at the particle/water interface (Fig. 3b). Dalcin et al. (2017) prepared DMY-loaded nanocapsules by insertion of DMY in polymeric nanoparticles. DMY-loaded nanocapsules not only demonstrated improved physicochemical properties (bioavailability) but also effective antimicrobial and anti-biofilm activity on urinary catheters infected by *Pseudomonas aeruginosa*. DMY-loaded nanocapsules reduced 67% of the biofilm population in urinary catheters in 96 h of treatment, while free DMY only eliminated 41%. Furthermore, a sustained release of DMY-loaded nanocapsule was observed as compared to free DMY. However, poor scalability, poor stability against aggregation and use of organic solvents are the major problems encountered during nanoencapsulation.

Microemulsion system is another popular formulation approach for solving the problems of low bioavailability. Microemulsion is a single optically isotropic and thermodynamically stable solution composed of drug, oil/lipid, surfactant, and/or co-surfactant with droplet sizes in the submicron range (Fig. 3c). (Lawrence & Rees, 2012). Solanki, Sarkar, and Dhanwani (2012) formulated a DMY microemulsion containing Capmul MCM (oil phase), Transcutol P (cosurfactant) and Cremophor EL (surfactant) in a ratio of 1:1.5:4.5, which attained maximal DMY content of 98.11%. DMY microemulsion showed higher drug release (72.34%) as compared to plain drug suspension (36.28%) and the commercially available tablet (46.91%), due to solubility-enhancing component of surfactant and cosurfactant. Despite the improvement in drug solubility and enhancement of bioavailability, micromulsions are not so effective in improving absorption because they have lower membrane permeability (Lawrence & Rees, 2012).

6.1.2. Cyclodextrin inclusion complex

Inclusion complexes prepared by kneading and co-evaporation methods exhibited higher dissolution efficiencies than their corresponding physical mixtures (Xu, 2015). Cyclodextrins as

Table 2

| BCS class | Solubility | Permeability | % Drug on market | % Drug on pipeline |
|-----------|------------|--------------|-----------------|-------------------|
| I         | High       | High         | 42              | 4.5               |
| II        | Low        | High         | 30              | 70                |
| III       | High       | Low          | 22              | 5.5               |
| IV        | Low        | Low          | 6               | 20                |

Fig. 3. Schematic representation of different formulation systems. a) solid dispersion; b) nano-encapsule; c) microemulsion; d) cyclodextrin inclusion complex; e) co-crystals; f) phospholipid complex; g) acylation.
pharmaceutical excipients are mainly used as solubilizing and stabilizing agents for lipophilic substances in aqueous preparations (Astray, Gonzalez-Barreiro, Mejuto, Rial-Otero, & Simal-Gándara, 2009; Suvarna, Gujar, & Murahari, 2017). DMY has been encapsulated in different substitutes of cyclodextrin to increase the solubility and dissolution rate (Fig. 3d). Solubility enhancement for DMY was 14.1-fold at 25 °C and 10.7-fold at 37 °C by forming inclusion complexes with β-cyclodextrin (β-CD) (Ruan et al., 2005). In another study of Liu, Li, et al. (2012) and Liu, Ma, et al. (2012), DMY was completely dispersed in the hydroxypropyl-β-cyclodextrin (HP-β-CD) matrix, the solubility of DMY in water increased from 0.74 to 53.64 mg/mL. The stability and antioxidant activity of DMY was greatly enhanced. Furthermore, Yang et al. (2011) also confirmed the solubility and stability enhancement of DMY in water by HP-β-CD; the inclusion complex not only affected the progress of the Human Hep G2 cell cycle but also induced cells to enter apoptosis. Recently, a systemic investigation of the inclusion complexation between different HP–CDs and β-CD with DMY was conducted by Liu, Li, Nguyen, and Zhao (2012). The stability of their inclusion complexes formed with different CDs followed the rank order: HP-β-CD (MW 1540) > HP-β-CD (MW 1460) > HP-β-CD (MW 1380) > β-CD > HP-γ-CD > HP-α-CD. Steric effect and hydrophobicity of the DMY was the major cause for the stability of the formed inclusion complex. The B ring of the DMY was most likely involved in hydrogen bonding with the side groups in the cavity of the CDs, through which the inclusion complex was stabilized. Although being a good solubilizing and stabilizing agents, cyclodextrins are prone to disruption and are coupled with lower apparent permeability.

### 6.2. Enhanced lipid solubility

#### 6.2.1. Phospholipid complexes

The technique of complexing bioactive molecules with dietary phospholipids has been developed for improving the bioavailability of plant extracts/actives with poor absorption (Alexander, Ajazuddin, Patel, Saraf, & Saraf, 2016; Hu, Liu, Zhang, & Zeng, 2017). Phospholipids act as an amphipathic molecules showing considerable solubility in both aqueous and lipid media (Fig. 3f). Besides, phospholipids are one of the major components of the cell membrane, which facilitates the permeation of the drug across the lipid-rich membrane without disturbing the cellular lipid bilayer, hence increasing its bioavailability (Khan, Alexander, AjazuddinSaraf, & Saraf, 2013; Zhang et al., 2016). Liu, Du, Jie, Chen, and Niu (2009) developed DMY-lecithin complex in order to improve the hydrophobicity of DMY. The solubility of DMY in n-octanol rose from 9.63 to 22.38 mg/mL. The lipophilic property of DMY was significantly improved due to DMY combination with lecithin by a non-covalent bond. Furthermore, the antioxidant performance of DMY was improved after being complexed with the lecithin. Phospholipid complex may be considered as a promising drug delivery system for improving the overall absorption and bioavailability of the plant flavonoid. However, low stability at acidic pH and high cost of raw materials limit its applications.
6.2.2. Acylation

In order to increase the solubility and stability of DMY in fatty phase, acylation of DMY (Fig. 3g) makes them more hydrophobic by fatty acid linkage, as reported in several studies (Guo et al., 2013; Li, Zheng, & Ning, 2005; Matsumoto & Tahara, 2001). Li et al. (2005) esterified DMY with lauroyl chloride, and the antioxidant activity of the obtained product (DMY-laurate) in lard oil was superior to that of DMY. Furthermore, the solubility and antioxidant activity of synthesized single-and multi-acylated DMY in peanut oil phase increased compared with DMY (Guo et al., 2013). However, chemical acylation is not regioselective and leads to an unwanted functionalization of phenolic hydroxyl groups. On the contrary, the enzymatic acylation of DMY has gained increasing attention due to its high efficiency, green process, mild reaction conditions and high regioselectivity. As for instance, enzymatic acylation of DMY was achieved by several lipases with fast reaction rate and high conversion yield (Li et al., 2015). Furthermore, Deng et al. (2016) designed a polydopamine-coated magnetic iron oxide nanoparticle (PD-MNPs) to immobilize Aspergillus niger lipase (ANL) to increase stability, reusability and catalytic performances of the lipase. The ANL@PD-MNPs was applied as a biocatalyst for the regioselective acylation of DMY in DMSO and gave a conversion of 79.3%, which was higher than that of previous reports (Li et al., 2015). Recently, Gao et al. (2017) used a novel deep eutectic solvent (DES)−DMSO cosolvent system as the reaction medium for enzymatic acylation of DMY catalyzed by ANL@PD-MNPs. The conversion of DMY was 91.6%. The lipid-solubility of DMY-16-acetate was 10 times higher than that of DMY. The lipase-catalyzed derivatives exhibited relatively strong radical scavenging abilities.

7. Conclusions and future trends

DMY is a bioactive flavonoid present in plant and various plant-based foods such as grapes and red bayberry. Both conventional and innovative methods including spectral and chromatographic methods have been reported for the identification and quantification of DMY in natural sources and biological samples. Numerous studies have reported diverse pharmacological activities of DMY, including antioxidant, antimicrobial anti-inflammatory, anti-cancer, anti-diabetic, and neuroprotective effects, etc. This indicates that DMY has a potential to be used as a nutritional supplement or the treatment of various diseases.

The phenol hydroxyl groups of DMY make it chemically unstable. Oxidation was reported as the main cause of changes in DMY. Avoiding metal ions, high temperature and alkaline conditions during processing and storage is important to minimize the degradation of DMY. DMY also faces with the problem of poor bioavailability, which limited its pharmacological effects and clinical application. To overcome this barrier, researchers have tried to use different strategies to enhance DMY solubility and bioavailability in both aqueous or lipid phase. Formulations based on solid dispersion, nanocapsule, microemulsion, cyclodextrin inclusion complexes, co-crystallization, phospholipid complexes, and chemical or enzymatic acylation have been proposed to increase lipid solubility. Understanding the mechanism of DMY absorption, metabolism and elimination is essential for evaluating its in vivo bioavailability efficacy. DMY digested in laboratory animals undergoes reduction, dehydroxylation, methylation, glucuronidation, and sulfation. On the basis of the current review, the future research needs for DMY should focus on the following three aspects: (i) development of new delivery systems for DMY to obtain higher encapsulation, overall absorption and bioavailability efficiencies; (ii) pharmacokinetic studies of encapsulated DMY such as absorption, distribution, metabolism and excretion in an in vivo setting on higher animals and humans; (iii) transformation of these encapsulated DMY into safe products providing health benefits for the consumer.

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A list of abbreviations

A. grossedentata Ampelopsis grossedentata

ANL Aspergillus niger lipase

API active pharmaceutical ingredient

β-CD β-cyclodextrin

BCRP breast cancer resistance protein

BCS biopharmaceutics classification system

BHA hydroxyanisole

BMI body mass index

CAT catalase activity

CE capillary electrophoresis

C NMR carbon-nuclear magnetic resonance

CXCR4 C-X-C chemokine receptor type 4

DAD diode array detection

DES deep eutectic solvent

DMSO dimethyl sulfoxide

DMY dihydromyricetin

DPPH 1,1-Diphenyl-2-picrylhydrazyl radical

2,2-Diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl

ESI-MS electrospray ionization mass spectrometry

FT-IR fourier transform infrared spectroscopy

GSH glutathione

HIV human immunodeficiency virus

H NMR Hydrogen-nuclear magnetic resonance

H2O2 hydrogen peroxide

HP-β-CD hydroxypropyl-β-cyclodextrin

HPCCC high-performance counter current chromatography

HPLC high performance liquid chromatography

HSCCC high-speed counter current chromatography

HUVECs human umbilical vein endothelial cells

iNOS inducible nitric oxide synthase

LC liquid chromatography

LDL low-density lipoprotein

LPS lipopolysaccharide

MCM microemulsion containing Capmul

MDA malondialdehyde

MIC minimum inhibitory concentration

MMP matrix metalloproteinase

MRP2 multidrug resistance protein 2

MS mass spectrometry

NF-kB nuclear factor-k-gene binding

NMR nuclear magnetic resonance

O2•− superoxide anion

OH• hydroxyl radicals

P eff effective permeability

PDH proline dehydrogenase

PD-MNPs polydopamine-coated magnetic iron oxide nanoparticle

PEG polymers polyethylene glycol

POV Peroxide value

PVP or polyvinylpyrrolidone

ROS reactive oxygen species

S. aureus Staphylococcus aureus

SOD superoxide dismutase

T-AOC total antioxidant capacity

TBHQ tertiary butylhydroquinone

TC cholesterol

TG triglycerides
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TLC thin-layer chromatography
UHPLC ultra-high performance liquid chromatography
UV ultraviolet
