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DRUG METABOLISM & DISPOSITION

# *Special Section on Natural Products: Experimental Approaches to Elucidate Disposition Mechanisms and Predict Pharmacokinetic Drug Interactions — Minireview*

# Natural Products as Modulators of CES1 Activity

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## ABSTRACT

**Carboxylesterase (CES) 1 is the predominant esterase expressed in the human liver and is capable of catalyzing the hydrolysis of a wide range of therapeutic agents, toxins, and endogenous compounds. Accumulating studies have demonstrated associations between the expression and activity of CES1 and the pharmacokinetics and/or pharmacodynamics of CES1 substrate medications (e.g., methylphenidate, clopidogrel, oseltamivir). Therefore, any perturbation of CES1 by coingested xenobiotics could potentially compromise treatment. Natural products are known to alter drug disposition by modulating cytochrome P450 and UDP-glucuronosyltransferase enzymes, but this issue is less thoroughly explored with CES1. We report the results of a systematic literature search and discuss natural products as potential modulators of CES1 activity. The majority of research reports reviewed were in vitro investigations that require further confirmation through clinical study. Cannabis products ($\Delta^9$-tetrahydrocannabinol, cannabidiol, cannabinol); supplements from various plant sources containing naringenin, quercetin, luteolin, oleanolic acid, and asiatic acid; and certain traditional medicines (danshen and zhizhuwan) appear to pose the highest inhibition potential. In addition, ursolic acid, gambogic acid, and glycyrrhetic acid, if delivered intravenously, may attain high enough systemic concentrations to significantly inhibit CES1. The provision of a translational interpretation of in vitro assessments of natural product actions and interactions is limited by the dearth of basic pharmacokinetic data of the natural compounds exhibiting potent in vitro influences on CES1 activity. This is a major impediment to assigning even potential clinical significance. The modulatory effects on CES1 expression after chronic exposure to natural products warrants further investigation.**

## SIGNIFICANCE STATEMENT

**Modulation of CES1 activity by natural products may alter the course of treatment and clinical outcome. In this review, we have summarized the natural products that can potentially interact with CES1 substrate medications. We have also noted the limitations of existing reports and outlined challenges and future directions in this field.**

## Introduction

The potential for pharmacokinetic interactions between natural products and conventional medications and the risks of associated therapeutic failure or toxicity continues to be a clinical concern (Johnson et al., 2018). To date, the vast majority of natural product–drug interaction (NPDI) research has focused on cytochrome P450 (P450) enzymes and UDP-glucuronosyltransferases (UGTs). However, there is accumulating literature implicating carboxylesterase (CES) 1 in NPDI. This review focuses on those reports.

Carboxylesterases have been isolated from diverse sources, including bacteria, fungi, algae, plants, animals, and humans. In humans, CES enzymes are classified into five subfamilies: CES1, CES2, CES3, CES4A, and CES5A (Holmes et al., 2010). CES1 and CES2 are the two primary forms that appear relevant to drug metabolism. Distinct differences between CES1 and CES2 have been identified relative to localization, substrate specificity, and gene regulation. CES1 is far more abundant in the liver than CES2, whereas CES2 predominates in the intestine (Hosokawa and Satoh, 1988; Imai et al., 2006). CES1 and CES2 are among the most abundant drug-metabolizing enzymes (DMEs) in the liver, constituting 42.9% and 1.4% of protein expressions of major phase I and phase II DMEs (i.e., P450s, UGTs, and CESs), respectively, in human liver microsomes (Fig. 1) (He et al., 2019). In the present review we have focused on CES1, which is involved in the biotransformation of the majority of therapeutic agents that are known CES substrates.

CES1 catalyzes the hydrolysis of various endogenous compounds (e.g., triacylglycerols) and xenobiotics containing structures of esters, amides, thioesters, and carbamates. In order of abundance, CES1 is primarily expressed in the liver, gallbladder, and lung (Hatfield et al.,

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**ABBREVIATIONS:** AA, asiatic acid; BDI, botanical-drug interactions; CBD, cannabidiol; CBN, cannabinol; CES, carboxylesterase; DME, drug-metabolizing enzyme; GA, gambogic acid; GLA, glycyrrhetic acid; HLM, human liver microsome [I]; the maximum plasma level of inhibitor encountered in vivo; NPDI, natural product–drug interaction; OA, oleanolic acid NPA; p-NPA para-nitrophenyl acetate; P450, cytochrome P450; TCM, traditional Chinese medicine; THC, $\Delta^9$-tetrahydrocannabinol; UA, ursolic acid; UGT, UDP-glucuronosyltransferase.

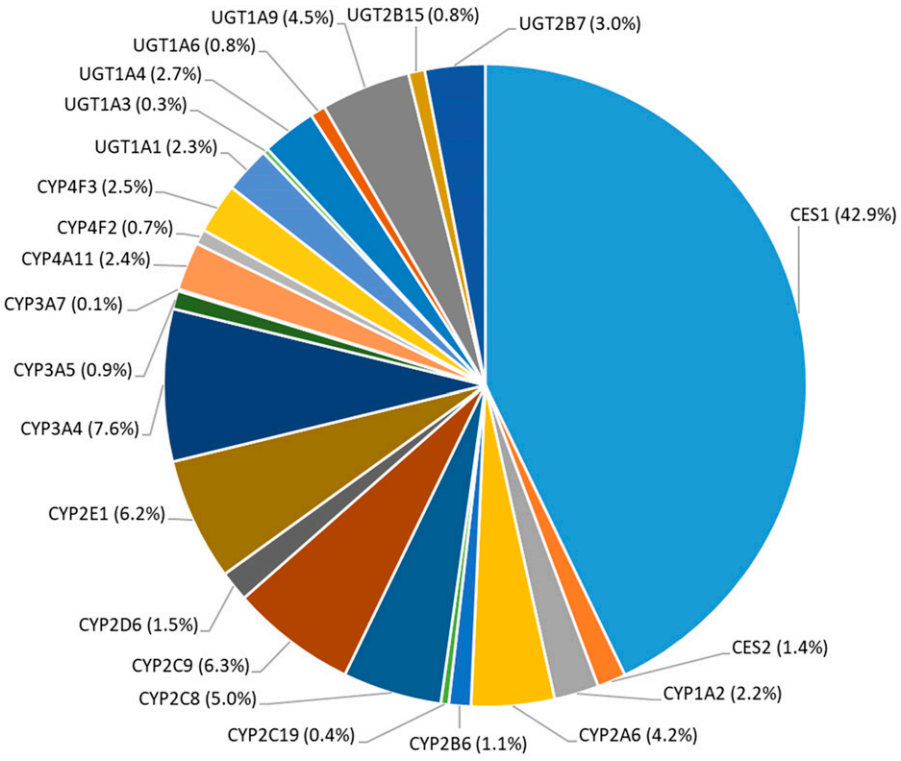


**Fig. 1.** Relative abundance of major DMEs in human liver microsome. The percentage values represent the relative quantities of individual enzymes in the major DMEs (i.e., P450s, UGTs, CESs) by molar unit. The molar values are derived from He et al. (2019).

2011; Di, 2019), and it is the predominant hydrolase in the liver, where it has been estimated to account for 80%–95% of its hydrolytic activity (Imai et al., 2006; Ross and Crow, 2007). Therefore, CES1 can be considered a major phase I DME and plays an essential role in the biotransformation of medications in both liver and lung. Indeed, drugs from almost all therapeutic classes (Table 1) have been identified as CES1 substrates (Her and Zhu, 2020). Depending on the structure and design of CES1 substrate medications, hydrolysis by CES1 either transforms a nonactive esterified prodrug (e.g., oseltamivir) into its active form (prodrug substrates identified in Table 1) or inactivates the pharmacologically active moieties (e.g., methylphenidate) by converting them into their inactive acid form. Among the molecular entities approved by the US Food and Drug Administration in the last decade, approximately 10% had "esterase" listed as their primary metabolic pathway (Drugs@FDA: FDA-Approved Drugs). When we examined the approval documents of these described esterase substrates, the majority did not specify the individual esterase, presumably because of the assumption of insignificant influence from a single esterase. However, an increasing number of research reports have documented that specific genetic mutations of the *CES1* gene result in impairment in CES1 activity, influencing both the pharmacokinetics and pharmacodynamics of its substrates. For example, a healthy volunteer participating in a pharmacokinetic drug interaction study of racemic (*dl*)-methylphenidate and ethanol was discovered to be carrying two previously undocumented *CES1* mutations, p.Gly143Glu (G143E) and p.Asp260fs, resulting in profound alterations in the metabolism and disposition of methylphenidate (Zhu et al., 2008). Notably, the $C_{max}$ of total methylphenidate was ~7-fold higher in this subject than the remaining participants. In other studies, individuals carrying the G143E mutation, a loss-of-function variant, were found to have higher exposure to the active metabolite of the antiplatelet drug clopidogrel combined with an enhanced pharmacodynamic (i.e., antiplatelet) effect (Lewis et al., 2013; Tarkiainen et al., 2015). In the Lewis study, single determination of the active metabolite concentration increased by 59% in the G143E carriers, along with a 24% in the reduction of platelet aggregation (Lewis et al., 2013). In the Tarkiainen study, the area under the concentration-time curve to infinite time ($AUC_{0\text{-inf}}$) and $C_{max}$ of the active metabolite were 67% and 63% higher, respectively, in subjects carrying the G143E variant. Consistently, the average platelet inhibition was 31% higher in the G143E subjects (Tarkiainen et al., 2015). Additionally, the requisite metabolic activation of the CES1 substrate and prodrug oseltamivir has been shown to be markedly affected by the G143E variant. This has been

TABLE 1

Substrates of CES1 as established by in vitro assay

| ACE Inhibitors | CNS Agents | Antihyperlipidemics |
|---|---|---|
| Benazepril[a] | Methylphenidate | Simvastatin[a] |
| Perindopril[a] | Flumazenil | Lovastatin[a] |
| Enalapril[a] | Cocaine | Clofibrate |
| Quinapril[a] | Rufinamide | Fenofibrate |
| Imidapril[a] | Heroin[a] | |
| Ramipril[a] | Meperidine | |
| Moexipril[a] | | |
| Trandolapril[a] | | |
| Antiplatelets/ Anticoagulants | Anticancer Agents | Chemical Warfare Agents |
| Clopidogrel[a] | Capecitabine[a] | Sarin |
| Dabigatran etexilate[a] | Irinotecan[a] | Soman |
| | Telotristat etiprate[a] | Tabun |
| Antiviral Agents | Immunosuppressive | Pesticides |
| Oseltamivir[a] | Mycophenolate mofetil[a] | trans-Permethrin |
| Sofosbuvir[a] | Ciclesonide[a] | para-Nitrophenyl valerate |
| Tenofovir alafenamide[a] | | |
| Endogenous Compounds | Miscellaneous | Synthetic Cannabinoids |
| Cholesterol | Oxybutynin | AB-PINACA |
| Fatty acid ethyl esters | Sacubitril[a] | AB-FUBINACA |
| | Selexipag[a] | PB-22 |
| | | 5F-PB-22 |

[a]Prodrugs.

demonstrated in vitro using cell lines stably transfected with the *CES1* variant (Zhu and Markowitz, 2009) as well as in single-dose clinical studies in healthy volunteer G143E carriers and noncarriers (Tarkiainen et al., 2012), suggesting that the therapeutic activity of this anti-influenza agent may be compromised in carriers. Indeed, one G143E homozygous subject had an $AUC_{0-inf}$ of the parent drug oseltamivir that was ~360% greater than that of noncarrier study peers. This striking difference highlights the potential therapeutic consequences of compromised CES1 activity in individuals treated with CES1 substrate medications.

Similarly, metabolic inhibition of CES1 by certain therapeutic agents or other substances including alcohol can lead to altered exposure to concomitantly administered CES1 substrates, such as methylphenidate and oseltamivir (Zhu et al., 2011; Patrick et al., 2013; Parker et al., 2015; Zhu et al., 2017). Thus, it is established that perturbations in CES1 activity can have clinical implications for patients treated with CES1 substrate medications.

Natural products broadly refers to the chemical compounds or preparations with a natural origin. These include foods, herbal or botanical medicines, and dietary supplements other than botanical products (e.g., vitamins). In many countries and cultures, notably China and India, herbs have been widely used and accepted in the practice of traditional medicine and carry a long and documented history of preparation and established pharmacopoeias for specific medical indications. These traditional medicines may be singular plant materials or extracts or complex mixtures of plant species. In the United States, the interest in and use of botanical supplements is far more recent, yet it has grown tremendously in the last two decades. Despite a required disclaimer of effectiveness for any medical indication on their labels, they are widely viewed as health-promoting by the United States lay public, and sales have been growing exponentially, reaching a total of $8.8 billion in the United States in 2018 (Gurley et al., 2018; Smith et al., 2019). However, botanical supplements require neither a rigorous development process, as is required for conventional medications, nor Food and Drug Administration scrutiny or approval prior to marketing. As a consequence, interactions between natural products and conventional medications are almost exclusively identified in the postmarketing period and take the form of adverse event case reports. Notable examples are grapefruit juice and Saint John's wort, which were found to exert potent inhibitory and inductive effect on the P450s, respectively (Bailey et al., 1998; Moore et al., 2000; Markowitz et al., 2003; Hanley et al., 2011; Bailey et al., 2013). Moreover, adverse events associated with the use of natural products may not be suspected, recognized, or efficiently reported by patients or physicians (Cellini et al., 2013), and potential use of multiple botanical products or botanical mixtures—a common practice—further complicates the issue. It is therefore essential to perform assessments of the potential for widely used botanical formulations to participate in significant botanical-drug interactions (BDI).

To date, the overwhelming number of published reports and investigations of BDIs involve the phase I P450 system and the phase II UGT enzyme system. Botanical influences on drug transporter activity have also been an area of investigation. Historically, relatively little has been explored or reviewed regarding the potential role of esterases in BDIs. However, in recent years, there has been a substantial increase in the number of published reports on putative BDIs implicating CES1. In the present review, we examine both in vitro and in vivo studies, with the aim of summarizing the methodology of studies carried out, their key findings, and when possible, identifying those natural products that can potentially modulate CES1 activity in a clinically significant manner under achievable exposure scenarios.

## Materials and Methods

Systematic literature searches were performed utilizing the MEDLINE and Embase databases. All pertinent studies, reviews, and case reports through February 2020 were retrieved. The search terms ("carboxylesterase 1" OR "CES1" OR "hCE1") AND ("drug-drug interaction" OR "drug interaction" OR "herb-drug interaction" OR "botanical-drug interaction" OR "inhibitor" OR "inhibition" OR "inducer" OR "induction") were incorporated. Articles were excluded if they were 1) not published in English; 2) not focused on the modification of CES1 activity by xenobiotics; and 3) not accessible in full text. Further refinement narrowed down studies to those involving natural products ($n$ = 16). Additional search terms ("carboxylesterase") AND ("drug-drug interaction" OR "drug interaction" OR "herb-drug interaction" OR "botanical-drug interaction") and cross-referencing of published bibliographies was also applied, yielding eight more articles of interest. In the final selection of articles, papers that solely presented animal studies ($n$ = 3) were excluded from this review, as animal models of drug interactions have limited translatability because of factors including interspecies differences in metabolism, the near-universal use of intraperitoneal dosing routes, and others. One report was also excluded because of the insufficient details provided, rendering a final total of 20 articles that were retrieved and reviewed. A flowchart of the systematic literature search was presented in Fig. 2.

The prediction of potential clinical interaction is made based on considerations of both the in vitro inhibition potency and the achievable clinical exposure of identified inhibitors. Since the in vivo concentration of a given inhibitor at an active or modulatory site is generally not known, its estimate is typically based upon available pharmacokinetic values, such as unbound or free concentration of the compound in plasma, with the assumption that it is this concentration presented to hepatocytes, P450, or other enzymes or transporters (Markowitz et al., 2008). However, with botanical constituents, there is an overall dearth of human pharmacokinetic data, which limits the ability to provide reliable estimates. Within this review, we assessed available pharmacokinetic studies of those compounds in humans and retrieved the maximum blood/plasma/serum concentration ($C_{max}$, [I]) values after their common routes of administration. The prediction was based on the ratio of $C_{max}$ ([I]) over the in vitro inhibition constant ($K_i$) or $IC_{50}$. A ratio value ([I]/$K_i$ or $IC_{50}$) between 0.1 and 1 indicates moderate interaction risks (Bachmann and Lewis, 2005; Wienkers and Heath, 2005; Zhang et al., 2009), and a value higher than 1 is considered of high interaction risk (Bachmann and Lewis, 2005; Wienkers and Heath, 2005). We consider a clinically significant interaction possible when either of the two risk categories is expected. Inhibitors that failed to achieve more than 50% inhibition were excluded from the assessment. Notably, many flavonoids were present in human blood/plasma/serum as both free compounds and their conjugated metabolites. The parent compounds and metabolites were not differentiated in most of the research reports, depending on the employed bioanalytical approaches. In our assessment, we focused on the free compound concentrations whenever possible. The total concentrations were used if the free concentrations were not available, with the assumption of equal inhibitory potency among the free compounds and their conjugated metabolites.

## Results

A total of 20 published reports were evaluated that involve assessment of approximately 36 herbal preparations or botanical extracts and more than 146 specific phytoconstituents. The majority of original research reports reviewed used one or more in vitro systems for data generation ($n$ = 19). However, one healthy human subject study was also identified. The in vitro assessments are summarized in Table 2. Botanical formulations or constituents with CES1-modulating activity were summarized into their respective chemical groups. For each natural product, results of in vitro and clinical drug interaction studies and their clinical exposure are provided.

### Cannabinoids

Cannabinoids are found in the plant cannabis (*Cannabis sativa* L.), a widely abused substance globally and in the United States. The use of recreational cannabis in the United States is widespread and increased

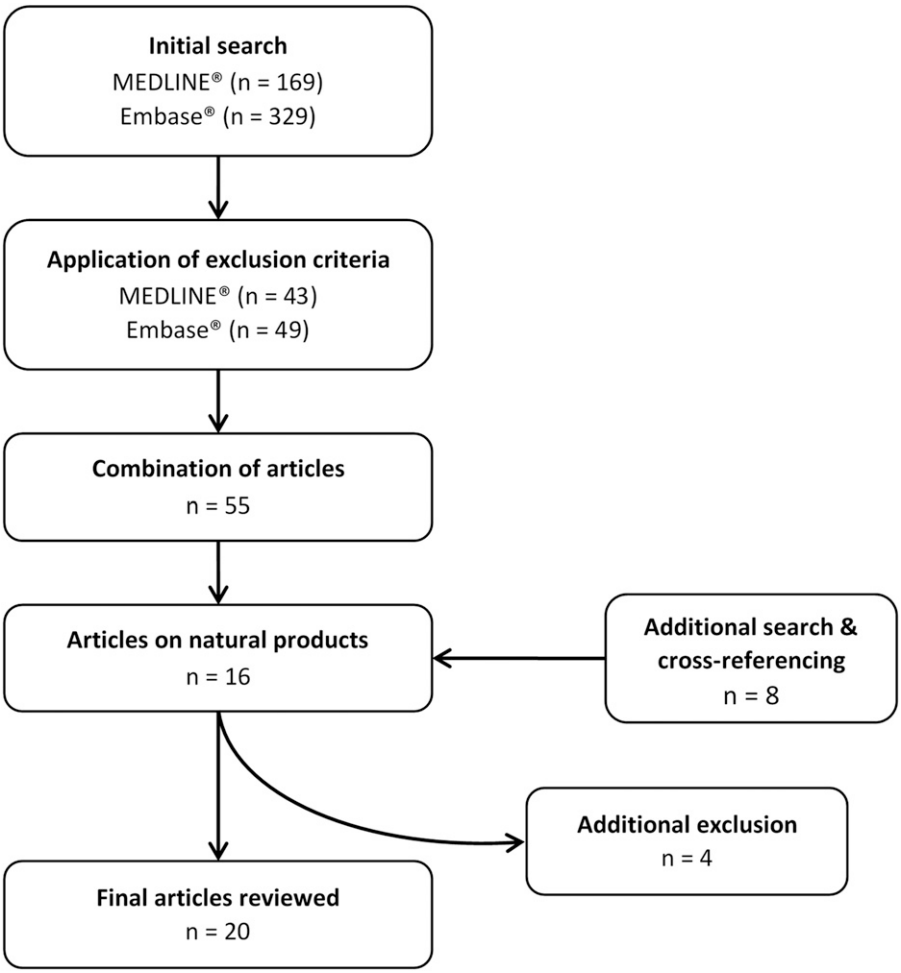


**Fig. 2.** Flowchart of systematic literature searches utilizing the MEDLINE and Embase databases.

significantly in the last decade (https://www.samhsa.gov/data/report/2018-nsduh-detailed-tables). Additionally, in the United States, there are presently 33 states as well as the District of Columbia that permit the use of "medical cannabis" or "medical marijuana" for one or more medical indications. The allowable form of cannabis or specific constituents as well as dosing routes differ from state to state. Most all of the states permit the use of medical cannabis in the treatment of diseases such as cancer, epilepsy, and human immunodeficiency virus/AIDS and numerous other chronic conditions (Bridgeman and Abazia, 2017). Thus, the presence and use of concurrent conventional medications with cannabis is commonplace. The ability of cannabinoids to interact with a variety of DMEs has been documented both in vitro and clinically (Cox et al., 2019; Qian et al., 2019a).

**In Vitro Studies.** The potential modulatory effects of three major cannabinoids on CES1 were assessed in a recombinant system by Qian et al. (2019b). All three cannabinoids [$\Delta^9$-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN)] exhibited potent in vitro inhibition, with $K_i$ values of 0.541, 0.974, and 0.263 μM, respectively. The study further showed an enhanced extent of CES1 inhibition by combining three major cannabinoids in the in vitro system, suggesting a higher than expected interaction risk after certain administration routes of cannabis products (e.g., smoking and vaping). Consistently, THC, CBD, and CBN were found to exert in vitro inhibition on the hepatic hydrolysis of heroin, a potentially concomitantly used substance and partial substrate of CES1 (Qian et al., 2020).

**Clinical Exposure.** The highest systemic exposure to THC appears to be achieved by recreational use (i.e., smoking) of cannabis cigarettes. In a study conducted by Huestis et al. (1992), a mean THC plasma $C_{max}$ of 162 ng/ml was observed in healthy males ($n$ = 6) after smoking a cannabis cigarette containing 3.55% THC. This observation was similar to several other pharmacokinetic studies (Lindgren et al., 1981; Perez-Reyes et al., 1982). The naturally occurring CBD and CBN are much lower in content than THC in cannabis products (Mehmedic et al., 2010), which leads to minimal exposure to them in the human body (Schwope et al., 2011; Desrosiers et al., 2014; Newmeyer et al., 2016). CBD has been developed as an oral solution (Epidiolex) for treatment of two severe forms of epilepsy in children, with which a significantly higher exposure was achieved ($C_{max}$ = 732 ng/ml after the second 750 mg twice-daily dose) (Taylor et al., 2018). When administered orally as a dietary supplement, measurable CBD concentrations were present in the blood circulation (Atsmon et al., 2018; Knaub et al., 2019; Patrician et al., 2019; Hobbs et al., 2020). The highest reported CBD exposure through this route ($C_{max}$ = 77.6 ng/ml) was observed in healthy males ($n$ = 12) after receiving 90 mg of CBD in a recently developed capsule formulation (Patrician et al., 2019). The highest documented CBN exposure was 11.6 ng/ml after smoking cannabis cigarettes (Newmeyer et al., 2016).

### Flavonoids

Flavonoids are a large family of polyphenolic plant compounds. Existing as secondary plant metabolites, there are six major subclasses of flavonoids: anthocyanidins, flavan-3-ols, flavonols, flavanones, flavones, and isoflavones. Flavonoids are found abundantly in nature within fruits, vegetables, grains, bark, roots, flowers, and some beverages, such

TABLE 2

In vitro assessments of modulatory effects of natural products on CES1

| | Representative Plants | Natural Compounds | System | Substrate | $K_i$ (μM) | $IC_{50}$ (μM) | Reference |
|---|---|---|---|---|---|---|---|
| Cannabinoids | *C. sativa* L. | $\Delta^9$-Tetrahydrocannabinol | rEnzyme | Oseltamivir | 0.541 | | Qian et al., 2019b |
| | | Cannabidiol | rEnzyme | Oseltamivir | 0.974 | | |
| | | Cannabinol | rEnzyme | Oseltamivir | 0.263 | | |
| Flavonoids | *Citrus paradise* (grapefruit) | Kaempferol | HLM | p-NPA | | 62 | Li et al., 2007 |
| | | | rEnzyme | p-NPA | 100 μM inhibited 68% hydrolytic activity | | Shimizu et al., 2014 |
| | | Naringenin | HLM | p-NPA | | 30 | Li et al., 2007 |
| | | Quercetin | HLM | p-NPA | | 43 | |
| | | | HLM | DME | | 33.43 | Wang et al., 2018b |
| | | | rEnzyme | p-NPA | 100 μM inhibited 81% hydrolytic activity | | Shimizu et al., 2014 |
| | | Galangin | HLM | p-NPA | | 81 | Li et al., 2007 |
| | | | HLM | DME | | 11.37 | Wang et al., 2018b |
| | | Morin | HLM | p-NPA | | 80 | Li et al., 2007 |
| | *P. corylifolia* (buguzhi) | Neobavaisoflavone | HLM | BMBT | 5.3 | | Sun et al., 2016 |
| | | Corylifolinin | HLM | BMBT | 9.4 | | |
| | | Coryfolin | HLM | BMBT | 1.9 | | |
| | | Corylin | HLM | BMBT | 0.7 | | |
| | | Bavachinin | HLM | BMBT | 0.5 | | |
| | *Radix et Rhizoma Glycyrrhizae* | Liquirtin | rEnzyme | Oseltamivir | 10 μM inhibited <50% oseltamivir hydrolysis | | Zhang et al., 2019 |
| | *S. baicalensis* | Wogonin | rEnzyme | p-NPA | 100 μM inhibited 58% hydrolytic activity | | Shimizu et al., 2014 |
| | Various plants | Luteolin | HLM | DME | | 5.34 | Wang et al., 2018b |
| | Various plants | Nevadensin | HLM | DME | 3.42 | 2.64 | |
| | Various plants | | HLM | BMBT | 3.57 | 2.58 | |
| | Various plants | Herbacetin | HLM | DME | | 68.01 | |
| Ginsenosides | *Panax ginseng*, *Panax notoginseng*, *Panax quinquefolius* (ginseng) | Dammarenediol II | HLM | DME | 2.1 | 1.99 | Sun et al., 2019 |
| | | 20*S*-*O*-*β*-(*d*-glucosyl)-dammarenediol II | HLM | DME | 2.4 | 1.76 | |
| | | Panaxadiol | HLM | DME | | 6.95 | |
| | | Panaxatriol | HLM | DME | | 34.93 | |
| Lignans | *M. officinalis* | Magnolol | HLM | DME | 0.34 | 0.35 | Song et al., 2019b |
| | | | HLM | BME | 0.23 | 0.21 | |
| | | | HLM | BMBT | 0.52 | 0.70 | |
| | | | HLM | Clopidogrel | 1.36 | 1.14 | |
| | *S. chinensis* (five-flavor berry) | Schisandrin B | HLM | BMBT | 29.8 | | Fu et al., 2019 |
| Tanshinones | *S. miltiorrhiza* (danshen) | Tanshinone IIA | rEnzyme | o-NPA | 6.89 | | Hatfield et al., 2013 |
| | | Tanshinone I | rEnzyme | o-NPA | 26.25 | | |
| | | Dihydrotanshinone | rEnzyme | o-NPA | 0.398 | | |
| | | Miltirone | rEnzyme | o-NPA | 2.53 | | |
| | | Cryptotanshinone | rEnzyme | o-NPA | 0.544 | | |
| Triterpenoids | Various plants | Oleanolic acid | HLM | DME | | 0.58 | Song et al., 2019a |
| | | | HLM | DME | | 0.28 | Zou et al., 2017 |
| | | Maslinic acid | HLM | DME | | 0.18 | Song et al., 2019a |
| | | Hederagenin | HLM | DME | | 0.37 | |
| | | Ursolic acid | HLM | DME | | 0.48 | |
| | | | HLM | DME | | 0.24 | Zou et al., 2017 |
| | | Corosolic acid | HLM | DME | | 0.33 | Song et al., 2019a |

(*continued*)

TABLE 2—*Continued*

| | Representative Plants | Natural Compounds | System | Substrate | $K_i$ (μM) | $IC_{50}$ (μM) | Reference |
|---|---|---|---|---|---|---|---|
| | | Pomolic acid | HLM | DME | | 0.73 | |
| | | Asiatic acid | HLM | DME | | 0.64 | |
| | | Polygalacic acid | HLM | DME | | 63.59 | |
| | | | HLM | DME | | 64.74 | Zou et al., 2017 |
| | | Glycyrrhetic acid | HLM | DME | | 17.25 | Song et al., 2019a |
| | | | HLM | DME | | 12.96 | Zou et al., 2017 |
| | | Betulinic acid | HLM | DME | 0.0564 | 0.015 | Song et al., 2019a |
| | | Betulin | HLM | DME | | 13.45 | |
| | | Betulinic acid-28-methyl ester | HLM | DME | | 0.32 | |
| | | Acetylbutulinic acid | HLM | DME | | 0.07 | |
| | | Celastrol | HLM | DME | | 4.43 | Zou et al., 2017 |
| | | Pachymic acid | HLM | DME | | 21.74 | |
| | | Dehydropachymic acid | HLM | DME | | 27.61 | |
| | | Polyporenic acid C | HLM | DME | | 58.6 | |
| Miscellaneous | *C. wightii* (guggul) | Z-guggulsterone | Human primary hepatocyte and Huh7 cell | | 0–20 μM induced both mRNA and protein levels of CES1 | | Yang et al., 2012 |
| | *G. hanburyi* | Gambogic acid | Huh7 and HepG2 cell | p-NPA | 0–0.75 μM decreased hydrolytic activity and protein level of CES1 | | Ning et al., 2016 |
| | *Handroanthus impetiginosus* (pau d'arco) | β-Lapachone | rEnzyme | o-NPA | 1.22 | | Hatfield et al., 2017 |
| | *Hydrastis canadensis* (goldenseal) | Goldenseal | HLM | Oseltamivir | Around 75% inhibition at single tested concentration (not specified). | | Liu et al., 2010 |
| | *Radix isatidis* | Epigoitrin | rEnzyme | Oseltamivir | 10 μM inhibited <50% oseltamivir hydrolysis | | Zhang et al., 2019 |
| | *Radix et Rhizoma Glycyrrhizae* | Glycyrrhizin | rEnzyme | Oseltamivir | 10 μM inhibited <50% oseltamivir hydrolysis | | |
| | Various plants | Sulforaphane | Human primary hepatocyte and Huh7 cell | | 10 μM induced mRNA of CES1 | | Chen et al., 2012 |
| | | Resveratrol | rEnzyme | p-NPA | 100 μM inhibited 60% hydrolytic activity | | Shimizu et al., 2014 |

BMBT, 2-(2-benzoyloxy-3-methoxyphenyl) benzothiazole; BME, 3,5-dimethyl BODIPY acid methyl ester; DME, D-luciferin methyl ester; HLM, human liver microsome; p-NPA, para-nitrophenyl acetate; o-NPA, ortho-nitrophenyl acetate; rEnzyme, recombinant enzyme.

as tea and wine. It has been estimated that >9000 unique flavonoids exist in nature, and many are believed to convey beneficial health properties, including antioxidant, antioncogenic, procardiovascular, anti-inflammatory, and antimicrobial activities (Ververidis et al., 2007; Ferrer et al., 2008). Flavonoids usually occur as glycosides in nature, which are hydrolyzed and absorbed in intestine after ingestion. The absorbed flavonoids are usually conjugated rapidly and appear in the circulation both as the free aglycone and conjugated forms.

Although the most common dietary sources of flavonoids are fruits and vegetables, flavonoids can also be found in a wide variety of herbs used in traditional medicines and within specific dietary supplements.

**In Vitro Studies.** The flavonoids in grapefruit (*Citrus* × *paradisi*) juice were investigated by Li et al. (2007) for their potential modulatory effects on esterases in human liver microsomes (HLM). Kaempferol, quercetin, morin, galangin, and naringenin inhibited the esterase activity, with $IC_{50}$ values ranging from 30 to 81 μM. Similarly, Shimizu et al. (2014) showed that 68% and 81% of the hydrolytic activity of recombinant CES1 was inhibited by 100 μM kaempferol and quercetin, respectively. In addition, the inhibitory effects of quercetin ($IC_{50}$ = 33.4 μM) and galangin ($IC_{50}$ = 11.4 μM) on CES1 were confirmed in an HLM system by Wang et al. (2018b).

Fructus psoraleae (buguzhi), a widely used traditional Chinese medicine (TCM) prepared as the dried ripe fruit of *Psoralea corylifolia* L., is commonly used for treatment of a diverse group of conditions, including vitiligo, cardiovascular diseases, osteoporosis, and nephritis. Many compounds have been isolated from fructus psoraleae, including flavonoids, chalcones, coumarins, monoterpenoids, and others (Zhou et al., 2019). In one investigation, the major flavonoids from fructus psoraleae (neobavaisoflavone, corylifolinin, coryfolin, corylin, and bavachinin) were identified as potent in vitro inhibitors of CES1, with $K_i$ values estimated as 5.3, 9.4, 1.9, 0.7, and 0.5 μM, respectively (Sun et al., 2016).

Several other naturally occurring flavonoids have also been found to modulate CES1 activity in vitro. In an HLM system, the flavones luteolin and nevadensin and the flavonol herbacetin inhibited CES1, with a range of $IC_{50}$ values varying from 2.6 to 68.0 μM (Wang et al., 2018b). The $K_i$ of nevadensin was further calculated as around 3.5 μM. In a study conducted by Shimizu et al. (2014), 100 μM wogonin, a flavonoid found in root extract of *Scutellaria baicalensis*, inhibited ~60% of the hydrolytic activity of a recombinant CES1 system.

**Clinical Exposure.** Naringenin can be measured in the systemic circulation after ingestion of various dietary sources, including orange juice, grapefruit juice, tomatoes, raisins, and certain herbs used in traditional medicine. Consumption of dietary naringenin via fruits and vegetables generally resulted in systemic concentrations below 200 ng/ml (Bugianesi et al., 2004; Gardana et al., 2007; Bredsdorff et al., 2010; Vallejo et al., 2010; Kanellos et al., 2013). Higher exposure was achieved by taking orange extracts or pure compound (Kanaze et al., 2007; Rebello et al., 2020). In a study reported by Rebello et al. (2020), after a single oral dose of whole-orange (*Citrus sinensis*) extract containing 600 mg of naringenin, a mean serum $C_{max}$ of 13.2 μg/ml was achieved in healthy volunteers ($n$ = 18). Notably, ingestion of grapefruit juice (8 ml/kg) was also able to yield relatively high plasma concentrations ($C_{max}$ = 1.6 μg/ml) (Erlund et al., 2001). A TCM formula known as zhizhuwan (a mixture of fruits from *Citrus aurantium* L. or *C. sinensis* Osbeck and roots from *Atractylodes macrocephala* Koidz) achieved a $C_{max}$ of 3.16 μg/ml in healthy volunteers ($n$ = 10) (Cao et al., 2010), whereas other tested traditional medicines generally rendered lower exposure (Xiong et al., 2014; Kitagawa et al., 2015b; Huang et al., 2019).

The bioavailability of quercetin has been extensively studied from a wide variety of sources, including onions, black tea, green tea, cranberry juice, sea buckthorn, apple, raisin, red wine, and pure compounds. Generally, ingestion of typical dietary portions achieved quercetin concentrations below 1 μg/ml in human (de Vries et al., 2001; Hollman et al., 2001; Goldberg et al., 2003; Suomela et al., 2006; Kanellos et al., 2013; McKay et al., 2015). However, relatively high $C_{max}$ of quercetin (1.1–2.3 μg/ml) was achieved in several studies after administration of onion supplement (331 μM quercetin glucosides), quercetin-4′-*O*-glucoside (331 μM isolated from onion), quercetin chews (RealFX Q-Plus providing 500 mg of quercetin), and dry shallot skin (1.4 mg of quercetin per kilogram) in healthy volunteers, respectively (Graefe et al., 2001; Wiczkowski et al., 2008; Kaushik et al., 2012). It should be noted that a relatively large variability in quercetin exposure has been observed between studies. Much lower systemic exposure to quercetin was observed in many other studies after onions or quercetin-containing supplements were administered (McAnlis et al., 1999; Erlund et al., 2000; Egert et al., 2008; Lee and Mitchell, 2012; Guo et al., 2014; Burak et al., 2017).

The systemic exposure to luteolin after ingestion of food supplements has been investigated in two independent studies using healthy volunteers. A plasma $C_{max}$ of 332 ng/ml luteolin was observed in healthy volunteers ($n$ = 8) after oral administration of *Chrysanthemum morifolium* extract (20 mg/kg) tablets (Li et al., 2013). In the second study, oral administration of an artichoke leaf extract (containing 35.2 mg of luteolin equivalents) yielded a plasma $C_{max}$ of 157 ng/ml luteolin in healthy volunteers ($n$ = 14) (Wittemer et al., 2005).

The exposure to kaempferol from several natural products has been investigated—namely, black/green tea, cranberry juice, sea buckthorn, red wine, onion, and raisins. The highest systemic level of kaempferol (397 ng/ml) was achieved 1 hour after consumption of sea buckthorn flavonols (Suomela et al., 2006).

### Ginsenosides

The name ginseng is variously applied to a number of different commercially successful herbs that have been used for centuries for their putative health benefits. Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are among the most popular products. Ginseng is generally consumed in an effort to improve overall well being, physical stamina, and immune function and to relieve a plethora of other health problems (Shergis et al., 2013). Ginsenosides are the major constituents found in ginseng.

**In Vitro Studies.** Sun et al. (2019) screened the inhibitory effects of more than 20 ginsenosides on CES1 utilizing an HLM system. Among the tested ginsenosides, dammarenediol II, 20*S*-*O*-β-(*d*-glucosyl)-dammarenediol II, panaxadiol, and panaxatriol exhibited $IC_{50}$ values <100 μM. Dammarenediol II and 20*S*-*O*-β-(*d*-glucosyl)-dammarenediol II had the most potent in vitro inhibition on CES1, with $IC_{50}$ values of 2.1 and 2.4 μM, respectively.

### Lignans

Lignans are a class of polyphenols in plants that may provide a number of health benefits, such as preventive effects from cancer, cardiovascular diseases, and diabetes (Durazzo et al., 2018). They can be found in various foods, such as seeds, whole grains, fruits, and vegetables (Adlercreutz, 2007).

**In Vitro Studies.** The bark of *Magnolia officinalis* has been used in traditional Chinese and Japanese medicine for more than 1000 years for treating various diseases, such as anxiety, depression, headache, asthma, and gastrointestinal disorders (Poivre and Duez, 2017). Magnolol is a bioactive lignan found in magnolia bark. In a study conducted by Song et al. (2019b), magnolol exerted potent inhibition ($K_i$ = 0.23–1.36 μM) on the hydrolysis of various substrates mediated by CES1.

*Schisandra chinensis* (Turcz.) Baill. is a further example of a botanical with a long history of use in TCM. This dietary supplement/medicinal

agent has been used in the treatment of diseases of the gastrointestinal tract, respiratory system, cardiovascular diseases, general fatigue and weakness, insomnia, and others. *S. chinensis* extracts contain numerous bioactive compounds, including lignans, triterpenes, phenolic acids, flavonoids, and polysaccharides, with the dibenzocyclooctadiene lignans purported to be responsible for many of the claimed health benefits (Nowak et al., 2019). Fu et al. (2019) evaluated the inhibition of CES1 by the major lignans isolated from the fruits of *S. chinensis* (Turcz.) Baill. Anwuligan, schisandrol B, schisanhenol, deoxyschizandrin, and schisandrin B were included in the assessment utilizing HLMs. Schisandrin B exhibited the strongest inhibition of CES1 activity, with a calculated $K_i$ of 29.8 μM.

### Tanshinones

The dried roots of *Salvia miltiorrhiza* (danshen) are commonly used in TCM as a single herb or in multiherb formulations for treatment of cardiovascular and cerebrovascular diseases (Cheng, 2007). Like most botanical extracts and formulations, danshen contains numerous phytoconstituents, with more than 100 components having been isolated and structurally identified to date (Su et al., 2015).

**In Vitro Studies.** Hatfield et al. (2013) demonstrated potent in vitro inhibition of recombinant CES1 by extracts of danshen roots. The extracts were further separated by chromatography, and the fraction showing the highest degree of enzyme inhibition was subject to mass spectrometry. Several tanshinones (tanshinone I, tanshinone IIA, and dihydrotanshinone) were identified as the major components, indicating their contribution to the inhibitory effects danshen extracts exhibited on CES1. When using the individual phytoconstituents, the inhibition potency of selected individual tanshinones were also evaluated in the recombinant enzyme system, with the calculated $K_i$ ranging from 0.398 to 26.3 μM.

**Clinical Exposure.** A pharmacokinetic study was conducted in healthy volunteers ($n = 24$) to compare exposure to tanshinones after a single oral dose of two different danshen formulations (traditional decoction vs. micronized granular powder) (Xing et al., 2017). The granular powder formulation resulted in much higher plasma concentrations of tanshinone I, tanshinone IIA, and cryptotanshinone, with mean $C_{max}$ values of 6.57, 25.8, and 146.7 ng/ml, respectively.

### Triterpenoids

Natural triterpenoids are phytochemicals that have wide distribution in various plants and are presented as free triterpenoids, triterpenic glycosides, phytosterols, and their precursors (Patlolla and Rao, 2012). Pharmacologically, the most significant triterpenoid structures are oleanane, ursane, lupine, and dammarane-euphane triterpenoids, which are frequently studied for their putative therapeutic properties, such anticancer, anti-inflammatory, and immunomodulatory effects (Dzubak et al., 2006).

**In Vitro Studies.** The inhibition of triterpenoids on CES1 has been reported by several studies (Zou et al., 2017; Song et al., 2019a) in which a panel of natural triterpenoids were screened in HLM. Pentacyclic triterpenoids, one of the major groups of these compounds, exhibited very potent inhibition, with $IC_{50}$ values generally under 1 μM. Those pentacyclic triterpenoids include oleanolic acid (OA), ursolic acid (UA), maslinic acid, hederagenin, corosolic acid, pmolic acid, asiatic acid (AA), betulinic acid, betulinic acid-28-methyl ester, and acetylbutulinic acid. Less potent in vitro inhibition ($IC_{50} > 1$ μM) was observed for several other triterpenoids, including polygalacic acid, glycyrrhetic acid [glycyrrhetinic acid (GLA)], betulin, celastrol, pachymic acid, dehydropachymic acid, and polyporenic acid C.

**Clinical Exposure.** The exposure to OA in humans has been studied from both supplements and daily food sources. The highest systemic concentration was reported by Rada et al. (2015), in which healthy subjects ($n = 9$) received a meal containing 30 mg of OA (dissolved in pomace olive oil). The serum $C_{max}$ of OA was achieved at 598 ng/ml. Interestingly, much lower exposure to OA ($C_{max}$ = 12 ng/ml) was observed in another study, in which a higher amount of OA (40 mg in capsules) was orally administered (Song et al., 2006). It was postulated that the oil formulation may assist with the absorption of OA in intestine. Besides intake of supplements, measurable OA was observed in systemic circulation ($C_{max}$ = 24 ng/ml) after ingestion of approximately 144 g of raisins (Kanellos et al., 2013). Only trace amount of OA was observed after consumption of apple peels and a traditional Japanese medicine (rikkunshito) (Kitagawa et al., 2015b; Stebounova et al., 2018).

UA has been proposed for treatment of various stages and types of cancers (Zou et al., 2019). Accordingly, a pharmacokinetic study was conducted in normal volunteers and patients with advanced solid tumors (Zhu et al., 2013). After intravenous administration of a nanoliposome formulation of UA in healthy volunteers ($n = 8$), a range of $C_{max}$ (1.84–3.46 μg/ml) was observed at three doses (37, 74, and 98 mg/m$^2$, respectively), which were well tolerated.

The exposure to AA was reported in two different studies of *Centella asiatica* derivatives. Grimaldi et al. (1990) reported a $C_{max}$ of 0.7 and1.36 μg/ml in healthy males ($n = 12$) after a single oral dose of 30 and 60 mg total triterpenic fraction of *C. asiatica*, respectively. A much lower $C_{max}$ of AA (38–117 ng/ml) was observed in a single- and multiple-dose study by Songvut et al. (2019), in which healthy volunteers ($n = 10$ to 11) sequentially took 250 and 500 mg of an extract of *C. asiatica* in two different periods, respectively.

Glycyrrhizin (or glycyrrhizinic acid or glycyrrhizic acid) is a triterpenoid saponin obtained from the root extracts of licorice (*Glycyrrhiza glabra*) and has been found to exert a wide range of biologic effects in vitro (Pastorino et al., 2018). After oral consumption, glycyrrhizin was mainly converted to GLA by intestinal microflora and absorbed (Kim et al., 2000; Ploeger et al., 2001). The pharmacokinetics of GLA in humans has been studied after administration of various formulations. The highest exposure to GLA in humans appears to be in a study reported by Krahenbuhl et al. (1994), in which healthy volunteers ($n = 6$) took a single oral dose of 500, 1000, and 1500 mg of GLA. The observed mean $C_{max}$ values of GLA were 4.5, 7.0, and 9.0 μg/ml, respectively. Several studies reported the administration of an ammonium salt of glycyrrhizin diammonium glycyrrhizinate to healthy volunteers (Ding et al., 2006; Zhao et al., 2008; Zou et al., 2009). After single oral doses ranging from 100 to 150 mg diammonium glycyrrhizinate, the achieved $C_{max}$ values of GLA were generally under 100 ng/ml. Similarly, a single oral dose of 75 mg of glycyrrhizin yielded a systemic GLA concentration of 200 ng/ml (Suzuki et al., 2017). GLA ingested as a component of traditional medicines has also been reported (Takeda et al., 1990; Kitagawa et al., 2015a; Sadakane et al., 2015; Lee et al., 2020), with the highest $C_{max}$ observed at 211 ng/ml. Glycyrrhizin has recognized antiviral effects in vitro and has been administered intravenously as a potential therapeutic agent for patients with hepatitis (Kumada, 2002; Manns et al., 2012; Hung et al., 2017). In a study conducted by Tanaka et al. (1993), patients with chronic hepatitis ($n = 8$) received repeated intravenous daily doses of 120 mg glycyrrhizin, which rendered 0.5–1.7 μg/ml of plasma GLA 2 hours after dosing.

An average serum celastrol level of 117 ng/ml was reported in patients ($n = 10$) with nephrotic syndrome 2 hours after ingestion of an extract from *Tripterygium wilfordii* Hook. F (20 mg) (Du et al., 2019).

In the study conducted by Kitagawa and colleagues, only a traceable amount of pachymic acid ($C_{max}$ = 91 pg/ml) was detected in healthy

adults ($n = 19$) who took oral 7.5-g doses of rikkunshito (Kitagawa et al., 2015b).

### Anti-Influenza TCM Formulas

In the theory of TCM, many symptoms caused by influenza are categorized as "exterior syndrome" and are usually treated with various formulas containing multiple herbs in combination as antiviral and immunomodulating agents. Therefore, those formulas are potentially coadministered with conventional anti-influenza agents, such as oseltamivir, a well recognized prodrug known to be activated by CES1.

**In Vitro Studies.** In an in vitro system comprising human recombinant CES1, Zhang et al. (2019) tested the inhibition of oseltamivir hydrolysis by 10 marker compounds from individual herbs used in the anti-influenza formulas. Epigoitrin, glycyrrhizin, and liquirtin at 10 μM were found to exert <50% inhibition.

**Clinical Studies.** In a 5-day-long clinical study ($n = 14$) conducted by Chang et al. (2014), 10 g of an anti-influenza TCM formula given twice daily did not significantly change the pharmacokinetics of oseltamivir in healthy volunteers.

### Miscellaneous

Guggul is a resin extract from *Commiphora wightii* that has been used in Ayurvedic medicine as a hypolipidemic agent (Deng, 2007). In a study conducted by Yang et al. (2012), both the mRNA and protein levels of CES1 were significantly induced in primary human hepatocytes treated with 10 μM of a major active phytosteroid (Z-guggulsterone) in guggul for 24 hours. The authors also tested the inductive effect of Z-guggulsterone in a human hepatic cell line (Huh7), and the induction on CES1 was found to be concentration-dependent (0–20 μM).

Ning et al. assessed the effects of gambogic acid (GA), a xanthonoid originated from *Garcinia hanburyi* and also present in the TCM gamboge, on carboxylesterases in two human hepatic cell lines (Huh7 and HepG2)(Ning et al., 2016). After being exposed to GA for 24 hours, the protein levels of CES1 were decreased concentration dependently in both cell lines, together with a decrease in the overall carboxylesterase activity as measured by p-NPA hydrolysis.

β-Lapachone is one of the naphthoquinones found in the inner bark of *Tabebuia avellanedae* (pau d'arco) and is marketed as an herbal supplement. This compound exhibited potent in vitro inhibition on recombinant CES1, with a $K_i$ value of 1.22 μM (Hatfield et al., 2017).

Sulforaphane is a natural chemical found in many cruciferous vegetables and is believed to have antioxidant and antitumor properties (Vanduchova et al., 2019). The induction of CES1 by sulforaphane was investigated by Chen et al. (2012), in which after a 24-hour exposure to 10 μM sulforaphane, significant increases (>2-fold) in CES1 mRNA level were observed in both human primary hepatocyte and the Huh7 cell line.

In a study conducted by Liu et al. (2010) screening traditional botanical medicines of the Cree indigenous population of northern Quebec, two extracts of unspecified composition exhibited approximately 50% inhibition on CES1-mediated oseltamivir hydrolysis in an HLM system. However, minimal inhibition was observed when they were prepared in a traditional way (i.e., 1 g dried material boiled in 250 ml water). In addition, goldenseal was found to achieve approximately 75% inhibition on oseltamivir hydrolysis in their assay system, although only a single concentration of goldenseal was tested.

Resveratrol is a popular and well studied dietary supplement product belonging to polyphenols. It has high antioxidant potential and exhibits anticancer properties in vitro, and it is of interest in treating a wide variety of inflammatory conditions (Ko et al., 2017; Nunes et al., 2018). Resveratrol was found by Shimizu et al. (2014) to inhibit 60% of CES1 hydrolytic activity in a recombinant system at a concentration of 100 μM.

**Clinical Exposure.** GA has undergone some development as an investigational anticancer agent in an intravenous formulation (Chi et al., 2013). After receiving a single intravenous dose (35 mg/m$^2$), the mean $C_{max}$ of GA in patients with cancer ($n = 6$) was determined to be 1.88 μg/ml (Ding et al., 2007).

Exposure to sulforaphane has most frequently been assessed in studies evaluating exposures after ingestion of broccoli or broccoli products. The highest documented exposure was 656 ng/ml after 200 μM of broccoli sprout extract containing sulforaphane was orally administered to patients with melanoma ($n = 5$) (Tahata et al., 2018).

Resveratrol has been extensively studied using various products formulated to enhance bioavailability, with the highest $C_{max}$ (1.94 μg/ml) reported in patients with cancer after oral administration of 5 g of micronized resveratrol (Howells et al., 2011).

## Discussion

Our review of the current literature indicated that a number of natural products appear to exhibit in vitro or clinical modulatory effects on CES1. To further assess the likelihood of an NPDI in humans, the potential clinical exposure to these potential CES1-modulating products was estimated by reviewing available pharmacokinetic studies and comparing these data to the respective in vitro parameters (e.g., $K_i$ and $IC_{50}$), as described in the *Materials and Methods* section. Figure 3 depicts the structures of those implicated compounds, and a summary of assessment was presented in Table 3, assuming clinical exposure scenarios that could produce the highest possible risk of NPDI. We considered a clinical drug interaction study as being warranted if a potential interaction was predicted in our assessment. A phase 0 study is warranted for compounds that showed in vitro inhibition but lacks pharmacokinetic data. A proposed priority list of natural compounds is presented in Table 4.

THC, CBD, and CBN can all potentially inhibit CES1 activity in certain clinical scenarios. A moderate interaction risk exists for THC and CBN ($[I]/K_i$ = 0.95 and 0.14, respectively) via recreational use (i.e., smoking or vaporizing) of cannabis cigarettes. The risk is higher for THC mainly because of its higher content (and thus higher exposure) in users of cannabis cigarettes. The systemic CBD concentration achieved by smoking cannabis is not likely to cause inhibition on CES1, as evidence by a $[I]/K_i$ value <0.012. However, a high and moderate interaction risk is expected through oral administration of CBD as Epidiolex ($[I]/K_i = 2.4$) and a dietary supplement ($[I]/K_i = 0.25$), respectively.

Moderate to high interaction risk is predicted for naringenin under various clinical occasions. Generally, consumption of fruits and vegetables does not produce sufficiently high naringenin concentrations in humans and is thereby free of interaction concerns ($[I]/IC_{50} < 0.03$). On the contrary, the $[I]/IC_{50}$ value is well above 1 after ingestion of whole-orange extract containing naringenin. Given the interest in its therapeutic effects on glucose and lipid metabolism, naringenin is likely to be taken in forms of botanical extracts or purified compounds, making the drug interaction plausible. In addition, grapefruit juice and the TCM formula zhizhuwan can also yield systemic concentrations of naringenin that are of moderate BDI risk. Besides naringenin, quercetin and luteolin are two other flavonoids that can have potential clinical interaction with CES1. Similar to naringenin, quercetin acquired from the consumption of a typical diet is of low BDI risk. However, it could theoretically produce a moderate inhibition of CES1 after the ingestion of quercetin supplements ($[I]/IC_{50} = 0.23$). Oral consumption of dietary supplements

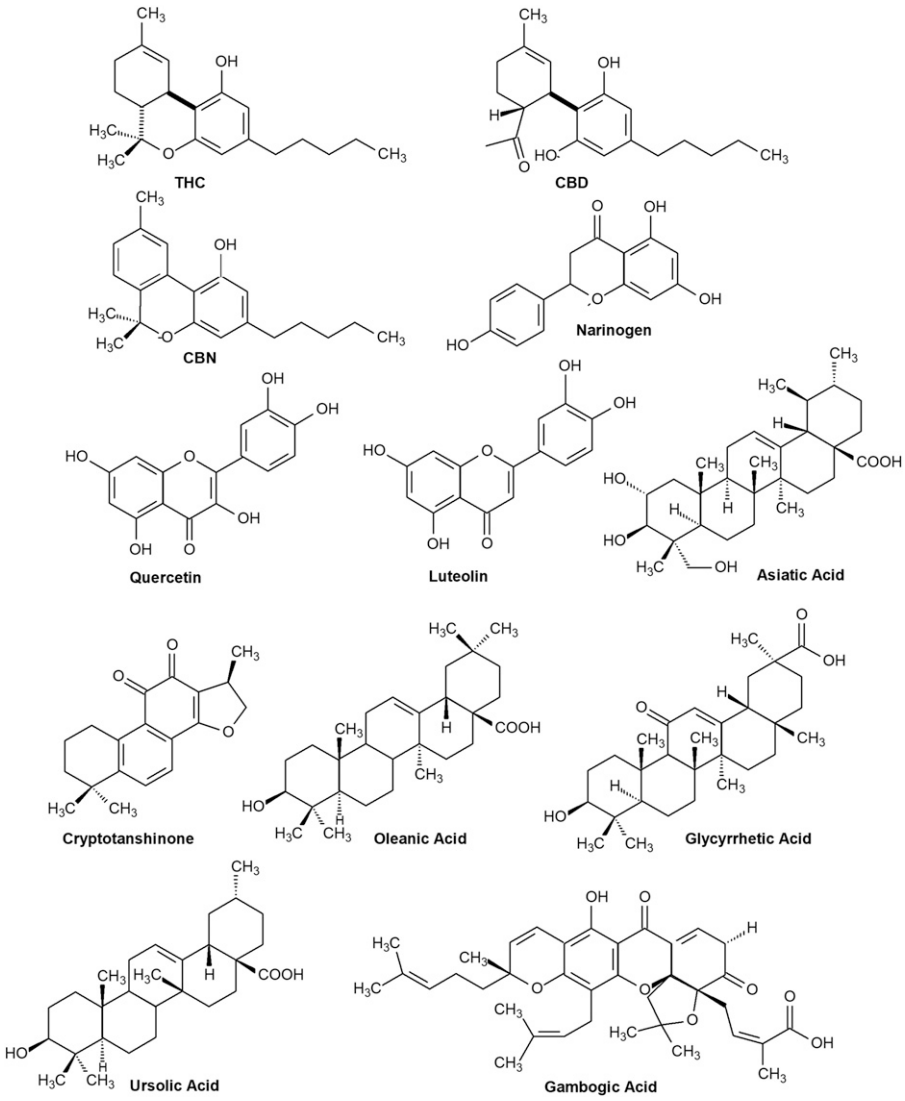


**Fig. 3.** Chemical structures of natural compounds that presently provide the strongest evidence of NPDI potential.

containing luteolin also appears to achieve sufficient systemic levels of luteolin exerting moderate inhibition on CES1 ($[I]/IC_{50} = 0.22$).

The risk of a clinical interaction between danshen and CES1 is considered moderate. This is mainly due to the presence of cryptotanshinone ($[I]/K_i = 0.91$) after the administration of a micronized granular powder formulation of Danshen. We were unable to find any documentation of human exposure to two of the identified tanshinones (dihydrotanshinone and miltirone); thus, their clinical inhibitory potential remains unknown and a matter of speculation. Interestingly, it appears that drug interactions caused by danshen products may be complex, and its modulatory effects on CES1 could be potentially masked. In a study of healthy volunteers conducted by Zhou et al. (2018), the clearance of clopidogrel and its active metabolite were significantly increased after a 7-day administration of danshen capsules. This result appears to contradict the results of the aforementioned in vitro study in that decreased CES1 activity would be anticipated to increase the exposure to clopidogrel and its active metabolite. Thus, the danshen-clopidogrel interaction may require further assessment with consideration to all DMEs contributing to clopidogrel biotransformation. Cryptotanshinone or tanshinone IIA has been further studied and found to induce the expression of CYP3A4 in a human hepatic cell line (HepG2). The observed phenomenon was concluded as a consequence of P450 induction by tanshinones. It is noteworthy that tanshinones were also found to exert modulatory effects on a variety of metabolic enzymes and transporters besides CES1 (Chen et al., 2017).

A high risk of NPDI is predicted for several triterpenoids for which very potent in vitro inhibition on CES1 (i.e., $IC_{50} < 0.64$ μM) was observed. Consumption of OA as a dietary supplement, especially taken with certain oil-based formulations, appears to represent the highest BDI risk ($[I]/IC_{50} = 4.7$). In addition, OA from raisins also has the potential to affect activity of CES1 in humans, although the extent is expected to be much lower ($[I]/IC_{50} = 0.19$). The exposure to AA has been studied after intake of *C. asiatica* supplements, which suggests a high potential of BDI when compared with the in vitro parameter ($[I]/IC_{50} = 4.3$). Notably, the studies also indicated that chronic consumption of *C. asiatica* supplements could lead to accumulation of AA in the circulation (Grimaldi et al., 1990; Songvut et al., 2019).

Although the intravenous administration of any botanically derived compound is uncommon, there are circumstances in which it does occur, and the implications are discussed accordingly. UA and GLA are two triterpenoids with which a clinical interaction could potentially occur after intravenous administration. The physiologic concentration of UA achieved after an intravenous dose well exceeds 1 ($[I]/IC_{50} = 32$), suggesting high risk of drug interactions. For GLA, its highest reported

TABLE 3

Notable examples of clinical exposure to natural products identified as CES1 modulators in studies with humanized in vitro system

| | Compounds | Exposure Routes | $C_{max}$ (μM)[a] | $K_i$ or $IC_{50}$ (μM) | [I]/$K_i$ or [I]/$IC_{50}$ | Reference |
|---|---|---|---|---|---|---|
| Cannabinoids | $\Delta^9$-Tetrahydrocannabinol | Smoking of a cannabis cigarette containing 3.55% THC ($n$ = 6) | 0.516 | 0.541 | 0.95 | Huestis et al., 1992 |
| | Cannabidiol | Second oral dose of 750 mg twice-daily Epidiolex ($n$ = 9) | 2.33 | 0.974 | 2.39 | Taylor et al., 2018 |
| | Cannabinol | Smoking of cannabis cigarettes containing 0.44% CBN ($n$ = 11) | 0.0374 | 0.263 | 0.14 | Newmeyer et al., 2016 |
| Flavonoids | Kaempferol | Consumption of an oatmeal porridge containing 78 mg of total sea buckthorn flavonols and 3 g sea buckthorn oil ($n$ = 11) | 1.39 | 62 | 0.02 | Suomela et al., 2006 |
| | Naringenin | Single oral dose of whole-orange extract containing 600 mg naringenin ($n$ = 18) | 48.4 | 30 | 1.61 | Rebello et al., 2020 |
| | Quercetin | Single oral dose of an onion supplement containing 160 g stewed and homogenized onions ($n$ = 12) | 7.64 | 33.4 | 0.23 | Graefe et al., 2001 |
| | Luteolin | Single oral dose of 20 mg/kg *Chrysanthemum morifolium* extract ($n$ = 8) | 1.16 | 5.34 | 0.22 | Li et al., 2013 |
| Tanshinones | Tanshinone I | Single oral dose of granular powder formulation containing 20 g crude danshen ($n$ = 24) | 0.0238 | 26.25 | <0.001 | Xing et al., 2017 |
| | Tanshinone IIA | Single oral dose of granular powder formulation containing 20 g crude danshen ($n$ = 24) | 0.0875 | 6.89 | 0.01 | Xing et al., 2017 |
| | Cryptotanshinone | Single oral dose of granular powder formulation containing 20 g crude danshen ($n$ = 24) | 0.495 | 0.544 | 0.91 | Xing et al., 2017 |
| Triterpenoids | Oleanolic acid | Consumption of a meal containing 70 g pomace olive oil with 30 mg dissolved oleanolic acid ($n$ = 9) | 1.31 | 0.28 | 4.68 | Rada et al., 2015 |
| | Ursolic acid | Single intravenous administration of a nanoliposome formulation of ursolic acid at 98 mg/m$^2$ ($n$ = 8) | 7.57 | 0.24 | 31.5 | Zhu et al., 2013 |
| | Asiatic acid | Single oral dose of 60 mg total triterpenic fraction of *C. asiatica* ($n$ = 12) | 2.78 | 0.64 | 4.35 | Grimaldi et al., 1990 |
| | Glycyrrhetic acid | Single oral dose of 1500 mg 18-$\beta$-glycyrrhetic acid ($n$ = 6) | 19.1 | 13.0 | 1.48 | Krahenbuhl et al., 1994 |
| | Celastrol | Twice-daily oral dose of 20 mg *Tripterygium* glycosides ($n$ = 10) | 0.26[b] | 4.43 | 0.06 | Du et al., 2019 |
| | Pachymic acid | Single oral dose of 7.5 g rikkunshito ($n$ = 19) | <0.001 | 21.7 | <0.001 | Kitagawa et al., 2015b |
| Miscellaneous | Resveratrol | Oral administration of 5 g micronized resveratrol ($n$ = 6) | 8.51 | 100[c] | 0.09 | Howells et al., 2011 |
| | Gambogic acid | Single intravenous dose (35 mg/m$^2$) of gambogic acid ($n$ = 6) | 2.99 | NA[d] | NA[d] | Ding et al., 2007 |
| | Sulforaphane | Once-daily oral dose of 200 μM broccoli sprout extract containing sulforaphane ($n$ = 5) | 3.70[e] | NA[d] | NA[d] | Tahata et al., 2018 |

[a]Mean peak plasma/serum/blood concentration, unless otherwise noted.
[b]Single determination at 2 hours after administration and calculated as the arithmetic mean of individual measurements.
[c]$IC_{50}$ was not calculated, and 100 μM (60% inhibition) was used in the calculation of [I]/$IC_{50}$.
[d]Compound that regulates expression of CES1.
[e]Single determination (mean value) at 2 hours after administration on day 1.

systemic level was achieved after the ingestion of capsules containing 500–1500 mg of pure GLA. However, such exposures are unlikely to occur under conditions of typical dietary intake. The use of licorice root extracts has been associated with several adverse effects, and consequently, a daily consumption below 100 mg of GLA is recommended (Omar et al., 2012). Daily oral intake of GLA from other sources (e.g., supplements, confectionery products, and traditional medicines) is generally not expected to affect CES1 activity ([I]/$IC_{50} \leq 0.04$). However, intravenously administered glycyrrhizin delivers high enough GLA that it is of moderate BDI risk ([I]/$IC_{50}$ = 0.28). UA and GLA are formulated as an intravenous dose because of their purported anticancer and antiviral effects, respectively (Kumada, 2002; Manns et al., 2012; Hung et al., 2017; Zou et al., 2019). Although the use of UA and GLA for these medical purposes is largely investigational at present, a significant risk of BDI is posed, requiring further research.

Beyond the aforementioned natural compounds and formulations, human pharmacokinetic studies have been conducted with the following compounds: kaempferol, celastrol, pachymic acid, and resveratrol. The existing pharmacokinetic studies do not support any of them being a clinical modulator of CES1 (i.e., [I]/$K_i$ or $IC_{50} < 0.1$). However, it should be noted that only one pharmacokinetic study is available for celastrol and pachymic acid. A higher physiologic concentration of these compounds may be attainable through consumption of other formulations that are as yet unstudied. If this is eventually documented to be the case, further assessment may be warranted at that time.

For natural compounds showing modulatory effects on the expression of CES1 (i.e., Z-guggulsterone, GA, and sulforaphane), the maximum inductive effects and the half-maximum inductive/inhibitory concentrations should be further investigated for a more accurate evaluation. Here, we made the assessment and judgment of whether existing literature supported the possibility of achieving the in vitro concentrations physiologically. No human pharmacokinetic study of Z-guggulsterone could be identified. The intravenous administration of GA may exert clinical effects on CES1, as suggested by an achieved systemic concentration of 3.0 μM ($C_{max}$), a concentration higher than that tested in the in vitro assay (0.75 μM), whereas sulforaphane only achieved a $C_{max}$ of 3.7 μM, which was well below the in vitro concentration (10 μM).

Subcellular systems (e.g., liver microsomes and recombinant enzymes) were employed in most of the in vitro studies reviewed. One major limitation of these systems is the inability to detect any effects from chronic exposure to the given natural products, which is a common practice in real life. Although we did not include any results of animal studies in this review, we are aware of the modulatory effects of one or more natural constituents from danshen and ginseng products on CES1 expression (i.e., downregulation) in Sprague-Dawley rat livers (Ma et al., 2018; Ji et al., 2019). Existence of such a mechanism may either

TABLE 4

Summary of clinical botanical-drug interaction potential of in vitro natural inhibitors

| Compounds with Moderate to High Interaction Risk (Need Clinical Interaction Study) | |
|---|---|
| $\Delta^9$-Tetrahydrocannabinol | |
| Cannabidiol[a] | |
| Cannabinol | |
| Naringenin[a] | |
| Quercetin | |
| Luteolin | |
| Cryptotanshinone | |
| Oleanolic acid[a] | |
| Ursolic acid[a] | |
| Asiatic acid[a] | |
| Gambogic acid[b] | |
| Glycyrrhetic acid | |
| Studied In Vitro but Lacking Pharmacokinetic Data for Interpretation (Need Phase 0 Study) | |
| Galangin | |
| Morin | Dihydrotanshinone |
| Neobavaisoflavone | Miltirone |
| Corylifolinin | Maslinic acid |
| Coryfolin | Hederagenin |
| Corylin | Corosolic acid |
| Bavachinin | Pomolic acid |
| Wogonin | Polygalacic acid |
| Nevadensin | Betulinic acid |
| Herbacetin | Betulin |
| Dammarenediol II | Betulinic acid-28-methyl ester |
| 20*S*-*O*-$\beta$-(*d*-glucosyl)-dammarenediol II | Acetylbutulinic acid |
| Panaxadiol | Dehydropachymic acid |
| Panaxatriol | Polyporenic acid C |
| Magnolol | $\beta$-Lapachone |
| Schisandrin B | Goldenseal (mixture) |

[a]High interaction risk as evidenced by a [I]/($K_i$ or $IC_{50}$) value >1.
[b]Regulates CES1 expression.

intensify or counteract the chemical interaction with CES1, highlighting the need of more-thorough research. Another consideration with chronic administration of natural products is the potential accumulation of phytoconstituents. Notably, many pharmacokinetic parameters (i.e., $C_{max}$) used in our assessments were measurements from single-dose exposure studies rather than at steady state. Thus, an underestimation of BDI liability is possible.

Several interaction studies on Sprague-Dawley rats were found but were not included in this review. Although animal models generally provide useful information, caution should be given when making direct clinical predictions. In the study conducted by Chang et al. (2014), the anti-influenza formula of TCM only exerted minimal impact on the pharmacokinetics of oseltamivir in healthy volunteers despite a positive interaction identified in rats. This observation highlights a potential interspecies difference in the pharmacokinetics of either the inhibitor, substrate, or both. The difference in tissue distribution and substrate specificity of carboxylesterases between human and other species has also been well established (Hosokawa, 2008; Lian et al., 2018; Wang et al., 2018a; Kisui et al., 2020). Notably, CES1 is found abundantly in the blood of rodents but not humans, representing a site of metabolism beyond the liver in rodents. In addition, both substrate and inhibitor can be differentially metabolized or transported between animal and human, which warrants the examination of interspecies difference of other DMEs and transporters when making such BDI predictions from animal studies.

It is a given that natural products contain a multitude of constituents. Many of the compounds from a plant source may exert similar or potentially additive or synergistic effects on an enzyme system or drug transporter in vitro, but the in vivo effects (if any) will be highly dependent on the bioavailability of each. In the case of the major cannabinoids THC, CBD, and CBN, all are generally detectable after smoking cannabis cigarettes, and all produce some degree of CES1 inhibition in vitro. Although the ultimate clinical effects on CES1 have yet to be evaluated, the possibility of additive effects must be considered. In another example, after the consumption of raisins, several flavonoids, including kaempferol, quercetin, and naringenin, were simultaneously present in plasma (Kanellos et al., 2013), each potentially contributing its own individual influence, suggesting the potential for additive influences on CES1 activity. Additionally, TCMs generally consist of a very complex mixture of botanicals so that concurrent exposure to multiple natural compounds ensues after administration. Therefore, a combination of modulatory effects by constituents should not be ruled out, nor the possibility of certain constituents producing opposite effects on an enzyme system in a somewhat "push-pull" influence, resulting in a net effect that is not easily predicted by existing models.

In conclusion, the available data on modulation of CES1 activity by natural products are limited compared with P450 and UGT assessments. However, there has been a recent accumulation of evaluable research reports. Not unexpectedly, published reports were primarily limited to results of in vitro investigations with almost no follow-up clinical assessments available. Although it cannot be emphasized enough that all in vitro findings must be confirmed by direct clinical assessment using appropriately designed studies, some potential CES1 interactions appear more likely than others. Moderate to high risk of clinical interactions was concluded by using cannabis products (THC, CBD, and CBN) via smoking or oral routes, supplements containing various flavonoids (naringenin, quercetin, and luteolin) and triterpenoids (OA and AA), and certain traditional medicines (danshen and zhizhuwan). In addition, UA, GLA, and GA when used intravenously are able to achieve systemic concentrations high enough to potentially cause a BDI. A clinical drug interaction study can be prioritized for these products. Many other natural compounds have been documented to exhibit potent CES1 inhibition ($K_i$ or $IC_{50}$ <1 $\mu$M) or induction in in vitro studies (corylin, bavachinin, magnolol, maslinic acid, hederagenin, corosolic acid,

pomolic acid, betulinic acid and its derivatives). However, we were not able to make similar statements about the potential clinical impact of these many compounds because of the lack of pharmacokinetic information on human exposures. A phase 0 study should be prioritized for these products. Lastly, several products appear to be able to modulate the expression of CES1 when administered chronically, an observation warranting additional study.

### Authorship Contributions

*Performed data analysis:* Qian, Markowitz.

*Wrote or contributed to the writing of the manuscript:* Qian, Markowitz.

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