Recent developments in formulation design for improving oral bioavailability of curcumin: a review

Zhenqi Liu, John D Smart, Ananth S Pannala*

5   Biomaterials and Drug Delivery Research Group, School of Pharmacy and

Biomolecular Science, University of Brighton, Brighton BN2 4GJ, UK

*Corresponding Author:

Dr Ananth S. Pannala FRSC

10   School of Pharmacy and Biomolecular Sciences

University of Brighton

Lewes Road

Brighton – BN2 4GJ

UK

15   Email: a.s.v.pannala@brighton.ac.uk

Tel: +44 1273 642 109

1

Abstract

Curcumin, a yellow-orange substance that is extracted from the spice turmeric (*Curcuma longa, Zinziberaceae*), has been attributed with a wide range of pharmacological activities for the prevention and treatment of several disease conditions such as arthritis, hypertension, diabetes, Alzheimer's, antibacterial and cancer to name a few. However, its potential for use as an orally delivered medicinal product is hindered by its poor solubility and bioavailability. The low oral bioavailability of curcumin is caused by several factors including low aqueous solubility, poor intestinal permeability, unstable at alkaline pH and rapid metabolism. To improve curcumin's poor oral bioavailability, different formulation strategies such as incorporation into nanoparticles, liposomes, micelles, micro/nano-emulsions and solid dispersions as well as co-administration with piperine have been investigated in both animal models as well as human supplementation studies. In this review, novel formulations of curcumin for oral delivery that were developed in recent years are reviewed and discussed.

Key words

1. Introduction

Curcumin is a yellow orange coloured crystalline compound that is extracted from the spice turmeric (*Curcuma longa, Zingiberaceae*). Chemically, curcumin is known as diferuloylmethane ($C_{21}H_{20}O_6$) with a molecular mass of 368.37 g/mol. It is a polyphenol compound and has a melting point of 183°C. The IUPAC name of curcumin is 1,7-bis (4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione (1E-6E). The two aryl rings in curcumin contain ortho-methoxy phenolic groups are symmetrically linked to a β-diketone moiety (Anand et al., 2007; Araiza-Calahorra et al., 2018; Carolina Alves et al., 2018; Esatbeyoglu et al., 2012). Curcumin exhibits a pH-dependent keto–enol tautomerism, where in an acidic or neutral solution, the keto form of curcumin is predominant while in an alkaline medium the enol form of curcumin becomes predominant (**Figure 1**) (Anand et al., 2007; Bernabé-Pineda et al, 2004; Jovanovic et al, 1999). The colour of curcumin also changes at different pH levels forming a bright yellow coloured solution at pH range 2.5 to 7.0 with the colour changing to dark red when the pH is increased above 7 (Anand et al., 2007; Esatbeyoglu et al., 2012).

The use of turmeric for medical treatment in Asia can be traced back thousands of years (Araiza-Calahorra et al., 2018). Turmeric has been widely used since ancient times as a herbal medicine for treating many conditions such as cough/inflammation, respiratory diseases, flu, sinusitis, liver disorders, rheumatism and abdominal pain (Ravindranath and

3

Chandrasekhara, 1980; Shoba et al, 1998; Wahlström and Blennow, 1978). In India, turmeric is traditionally used for treating infections, sprains/swelling and healing burn wounds (Araujo et al., 2001), while in China turmeric is regularly

65 used as herbal medication for treating diseases that are associated with abdominal pain (Aggarwal et al., 2004). With the advancement of science and technology, it had been discovered that curcumin is the key ingredient that contributes to most of the therapeutic effects of turmeric (Mukundan et al., 1993; Pal et al., 2001). Curcumin was found to have a wide spectrum of

70 pharmacological activities. Several studies on curcumin showed that it has anti-inflammatory (Srimal and Dhawan, 1973), antimicrobial (Kim et al., 2003; Kuttan et al., 1985; Prasad et al., 2015; Reddy et al., 2005), antirheumatic (Senft et al., 2010), immunomodulatory (Jantan et al., 2011) and anti-tumour effects (Hatcher et al., 2008). The anti-tumour effect of curcumin is associated

75 with the suppression of early growth of response-1-gene product (EGR-1), protein tyrosine kinase cascade and mitogen-activated protein kinases (MAPK) pathway (Khan et al., 2018). Curcumin also demonstrates antioxidant property based on its ability to scavenge free radicals due to the electron donating property of the phenolic group (Khopde et al, 1999; Masuda et al.,

80 2001; Ruby et al., 1995; Sharma, 1976; Sugiyama et al., 1996). The anti-inflammatory effect of curcumin is associated with its ability to inhibit NFκB (Nuclear factor κB) to bind with DNA. The inhibition of NFκB-DNA binding lead to suppression of pro-inflammatory molecules MMP-3 (matrix metalloprotease

3) and MMP-9 (matrix metalloprotease 9). It also results in reduction in pro-

85   inflammatory cytokines, such as TNFα (tumor necrosis factor 1α), IL1β

(interleukin 1β) and IL8 (interleukin 8) (Esatbeyoglu et al., 2012). In addition,

curcumin also exert anti-inflammatory effects by binding to proteins COX-2

(prostaglandin-endoperoxide synthase 2), which leads to reduction in COX-2

expression, prostaglandin and thromboxane synthesis. Subsequently,

90   curcumin inhibits the activity of 5-LOX (Arachidonate 5-lipoxygenase) and

leukotriene synthesis. The decreased expression of these compound

attributes to the anti-inflammatory effects of curcumin (Hong et al., 2004). The

anti-bacterial effect of curcumin is believed to be associated with its ability to

inhibit the formation of FtsZ ring (Z ring) at the site of division of bacterial cells,

95   which disrupts the division of the bacterial cells (Rai et al., 2008). Curcumin

also showed anti-viral effect on several viruses such as HIV, influenza, HSV-1,

coxsackievirus and HBV. The anti-viral activities of curcumin include inhibiting

the HIV-1 LTR-directed gene expression, HIV-1/HIV-2 proteases,

haemagglutination, reducing HSV-1, coxsackievirus and HBV replication.

100   (Moghadamtousi et al., 2014). The pharmacological effect of curcumin on

rheumatic diseases like osteoarthritis is based on its ability to in inhibit the

expression of metalloproteinase-3 enzymes (MMP3). MMP3 is highly

expressed in synovial cells in patients with osteoarthritis, which results in the

degradation of connective tissue components. By inhibiting the expression of

105   MMP3, curcumin inhibits the proliferation of osteoarthritis synovial cells,

increases the cell apoptosis, and eventually ease the inflammation and cartilage degradation of osteoarthritis (Yang et al., 2019). Although the exact mechanisms are still unknown, the immunomodulatory effects of curcumin are most likely due to its ability to inhibit NF-κB target genes that are involved in

110 inducing immune responses (Yadav et al.,2005). Additionally, activity in protecting the heart and kidney against oxidative injury was reported in several studies (Saeidinia et.al., 2018; Venkatesan, 1983, Venkatesan, 2000, Venkatesan et al., 2000). Curcumin shows heart protecting effect through several mechanisms that include inhibiting cardiomyocyte fibrosis, increasing

115 ventricular hypertrophy and related-gene expression (Saeidinia et.al., 2018). Curcumin protects against renal injury by inhibiting lipid peroxidation in kidneys, which reduces oxidative injury to the kidneys. It also increases levels of natural antioxidants, kidney glutathione content and glutathione peroxidase activity in kidney tissues, which restores kidney functions (Venkatesan, 2000).

120 Curcumin also showed therapeutic activity in diabetes due to its effect in increasing sensitivity to insulin and reducing blood glucose levels in humans (Parsamanesh et al., 2018). Other studies showed that curcumin could be a promising drug candidate for treating or preventing neurodegenerative diseases such as Alzheimer's disease (AD) (Mutsuga et al., 2012; Ray et al.,

125 2011), Parkinson's disease (PD) and brain tumours (Hatcher et al., 2008; Mythri et al., 2011). It has been reported that curcumin suppresses the formation of amyloid β protein aggregates in the brain. The suppression of

amyloid β protein aggregates leads to the reduction of reactive oxygen

species (ROS) and cytochemokines, which decreases oxidative stress

130 induced damage and neuroinflammation to the brain (Mutsuga et al., 2012;

Mythri et al., 2011; Ray et al., 2011).

The safety of curcumin was proven in several animal tests and human

studies (Lao et al., 2006a, 2006b; Sharma et al., 2004; Siviero et al., 2015).

An oral dose as high as 12g per day was shown to be well tolerated in

135 humans (Lao et al., 2006b). However, despite its wide pharmacological

potentials and high dose tolerance, curcumin is still not approved as a

therapeutic agent for oral delivery. The main reason is because curcumin has

very poor oral bioavailability so it can be barely absorbed in the human body

(Anand et al., 2007). Curcumin plasma concentration was under the detection

140 limit at an oral dose of 12 g in healthy male subjects (Klickovic et al., 2014). To

overcome curcumin's problem of bioavailability, numerous research studies

have been reported every year. In this review, factors that account for the poor

oral bioavailability of curcumin are first explained in detail followed by a review

of recent efforts in improving curcumin's oral bioavailability.

145

2. Routes of drug administration reported for curcumin

The delivery routes of curcumin include oral administration, intravenous (IV)

injection, nasal administration, topical administration, subcutaneous delivery

and intraperitoneal (IP) administration (Prasad et al., 2014).

150   Among the delivery routes, oral delivery is regarded as the most accepted

route for drug administration. It is also the most preferred administration

routes over other delivery routes due to its convenience, high patient

compliance, cost effectiveness and ease of production (Gupta et al., 2009).

Besides, oral administration is the most studied delivery route for curcumin. In

155   most of studies, curcumin was delivered to the subjects (either humans or

animals) through oral administration (Prasad et al., 2014). Orally delivered

curcumin has exhibited various pharmacological effects such as anti-

inflammatory, anti-tumor, antioxidant, antimicrobial, antidiabetic,

immunomodulatory, etc.

160   In IV administration, curcumin is injected directly into blood vessels, which

helps curcumin bypass the physiological barriers against drug absorption,

leading to highest bioavailability and fastest effect among all delivery routes.

However, compared with the oral route, IV injection has some major

drawbacks such as poor patience adherence, inconvenience, needle-

165   associated pain, risk of unsafe needle use and the need for trained healthcare

personnel (Homayun et al., 2019).

    Topical delivery is administration of drugs directly on to the body surfaces

such as skin or mucous membranes. Compared with oral administration,

curcumin delivered though topical route showed pharmacological effects

170   related mostly to the skin conditions such as skin inflammation, wound healing

and skin cancer among others (Dovigo et al., 2013; Lopez-Jornet et al.,2011;

LoTempio et al, 2005; Sun at al., 2013).

Nasal delivery is a drug administration route where the drug is insufflated through the nose and absorbed *via* the nasal mucosa. Curcumin was used in nasal administration for better brain targeting and it showed pharmacological effects on neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (Prasad et al., 2014). Nasal delivery is an easier way for delivering curcumin when compared with IV injection. However, it is still relatively inconvenient when compared to oral delivery route since there is a possibility of nasal irritation for some patients (Türker et al., 2004).

Intraperitoneal injection is an administration route where the drug is injected direclty into the peritoneum (body cavity) and in subcutaneous injection the drug is injected into the tissue layer between the skin and the muscle. These two delivery routes were reported more often and used in the administration of curcumin to animals than to humans (Prasad et al., 2014).

The routes of administration played important roles in the therapeutic effects of a drug substance. Among all the delivery routes of curcumin, oral administration is an effective route to deliver curcumin with numerous advantages over other administration routes. Therefore, it is suggested to focus more on the studies of oral administration of curcumin and the development of curcumin formulation for oral delivery.

3. Factors that account for curcumin's poor oral bioavailability

According to the Biopharmaceutics Classification System (BCS), curcumin could be classified as a class IV substance since it has poor aqueous solubility and limited permeability across the intestinal membranes (Paolino et al., 2016). Apart from the poor solubility and intestinal permeability, curcumin also has low serum concentration, poor pH dependent aqueous-stability and rapid metabolism in animals and humans, which are believed to be the main reasons that account for the poor oral bioavailability of curcumin. (Gantait et al., 2001; Holder et al., 1978; Ireson et al., 2001; Kunnumakkara et al., 2008; Kurien et al., 2007; Modasiya and Patel, 2012; Murugan and Pari, 2006; Perkins et al., 2002; Pfeiffer et al., 2007; Ravindranath and Chandrasekhara, 1981; Sandur et al., 2007; Song et al., 2016; Suresh and Nangia, 2018; Tønnesen and Karlsen, 1985; Wang et al., 1997).

3.1. Poor aqueous and gastro-intestinal fluid solubility

Curcumin is hydrophobic so it has extremely poor water solubility (Lao et al., 2006b). Its aqueous solubility is also pH dependent. At acidic or neutral pH, it is practically insoluble. The maximum solubility of curcumin in aqueous solution at pH 5 was only 11 ng/ml (Gantait et al., 2001; Song et al., 2016). It was reported that the solubility increased to 0.1 μg/ml at pH 6.8. However, it dropped to 0.06 μg/ml when the pH was increased to 7.4 (Modasiya and Patel, 2012). For any orally administrated drug to be absorbed, it needs to

10

215 dissolve in the gastrointestinal (GI) fluids. GI solubility of curcumin tested in

simulated gastroenteric fluids reported that curcumin showed equilibrium

solubility of 2.5μg/ml in the fasted simulated gastric fluid((pH1.6), 3μg/ml in

simulated gastric fluid (pH1.2) and 2μg/ml simulated intestinal fluid (pH6.8)

(Jaisamut et al., 2013). Compared with the solubilities tested in water or buffer

220 solutions, curcumin solubilities measured in simulated gastroenteric fluids

seems to be much higher but still quite low. This reason for the higher

solubilities tested in the simulated gastroenteric fluids is unknown but it might

be due to the presence of pepsin in the simulated gastroenteric fluids. There

were studies which showed that pepsin can improve the solubility of lipophilic

225 drugs although the mechanisms behind have not been founded yet

(Nascimento et al., 2012; Pinnamaneni et al., 2015).

Curcumin has a low plasma concentration even after administering a high

oral dose. A clinical trial conducted in healthy human males even after an oral

dose of curcumin as high as 12 g the plasma curcumin concentration was too

230 low to be detected (Klickovic et al., 2014).

In contrast, when 1 g/kg of curcumin was delivered orally to Sprague–

Dawley rats and measuring plasma curcumin concentration showed that the

amount of curcumin present in the plasma was less than 1% of the

administrated dose (Wahlström and Blennow, 1978). A similar result was also

235 reported by Chang et al (Chang et al., 2013), after an oral dose of 1 g/kg of

curcumin in rodents resulted in curcumin plasma concentration of 15 ng/ml

after 50 min (Chang et al., 2013).

When at the same dose, human showed much lower curcumin plasma concentration than rats. The same dose of curcumin (2 g/kg) was delivered orally to rats and humans respectively. The maximum plasma concentration (Cmax) in rats was found to be 1.35 ± 0.23 µg/ml measured 50 min after taking the dose, whereas the Cmax of curcumin in humans was only 0.006 ± 0.005 µg/ml measured 1 hour after administration (Shoba et al, 1998).

The results from these studies further suggests that curcumin has a very poor plasma concentration even after a high oral dose in both rodents and humans. When the same oral dose was administered, rats were found to have higher plasma concentration of curcumin than humans.

3.2. Low permeability (absorption)

Apart from solubility, permeability is another main factor that affect oral drug administration since the absorption of drugs depends on its permeability across the biological membrane of the GI tract after dissolution (Parikh et al., 2016). Experimental results in *in vivo* animal models and simulated human intestinal epithelium barrier have shown that curcumin is poorly permeable across intestinal membranes even after dissolution (Gao et al., 2013; Righeschi et al., 2016; Volpe et al., 2007; Wahlang et al., 2011). It was found that in the rat small intestine, curcumin was best absorbed at the duodenal segment, followed by the jejunum and colon. The absorption of curcumin in

the ileum was the poorest (Wang et al., 2017a).

Caco-2 cell lines (**Figure 2**) possess the same cell polarity and compact single-cell layer just like human intestinal epithelial cells and as a result, they are commonly used as the cell model for testing the intestinal permeability/absorption of drugs (Artursson and Karlsson, 1991; Parikh et al., 2018a; Sambuy et al., 2005; van Breemen and Li, 2005; Volpe et al., 2007; Xue et al., 2017). The results from permeability test for curcumin reported by Zeng et al. (Zeng et al., 2017a) in Caco-2 cell lines exhibited that there was a decrease of permeability from the apical side to the basolateral side (A to B direction) with an increase in curcumin concentration. Conversely, permeability from the basolateral side to the apical side (B to A direction) increased along with an increase in the concentration of curcumin added. Furthermore, curcumin at concentration of 5 µg/ml, the value of PappA-B was greater than PappB-A which indicated an increased absorption of curcumin. However, when the curcumin concentration was increased to 10 µg/mL and 20 µg/ml, the value of PappA-B became lower than PappB-A ,indicating that the amount of curcumin that is being pumped out from the cells is higher than the amount being absorbed at this concentration range. It also showed that the intestinal permeability of curcumin does not increase in a concentration dependent manner for curcumin (Zeng et al., 2017a).

In transcellular studies, apparent permeability coefficient (Papp) was used to represent the amount of compound transported per unit time (Wang et al.,

13

2017a). It was reported that the value of Papp is correlated to the extent of drug molecules that penetrate across the intestinal tract of the drugs (Artursson and Karlsson, 1991; Ozeki et al., 2015;). However, in another curcumin permeability study conducted using Caco-2 cell line it was reported

285 that efflux pathways do not play a role in curcumin intestinal permeability. This observation was based on Papp (A to B) value (2.93 ± 0.94 x 10^{-6} cm/s) was found higher than the value of Papp (B to A) (2.55 ± 0.02 x 10^{-6} cm/s) at curcumin concentration of 62.6 µg/ml (170µM), (Wahlang et al., 2011).

An efflux pump like P-glycoprotein could also affect the permeability of

290 curcumin. P-glycoprotein is an ATP dependent efflux pump that can pump drugs out of the cells thus reducing the bioavailability. In the small intestine, the expression of P-glycoprotein is present at ileum and jejunum (Canaparo,2007). An in vitro study using Caco-2 cells showed that co-administration of P-glycoprotein inhibitor such as verapamil, along with

295 curcumin could increase the rate absorption of curcumin (Xue et al.,2017). This indicated that curcumin could potentially be a P-glycoprotein substrate and blocking P-glycoprotein can help to improve the permeability as well as the drug absorption in the intestinal tract. Wand et al (Wang et al., 2017a) have investigated a concentration dependent effect of verapamil on the

300 absorption of curcumin in rat intestines. No obvious change to the absorption of curcumin was observed when verapamil concentration was increased from 0.05 mmol/L to 0.1 mmol/L. When verapamil concentration was increased to

14

0.5 mmol/L, the rate of curcumin absorption was increased by approximately

3%. This showed that P-glycoprotein inhibitor like verapamil is capable to

305   improve both the rate and the amount of curcumin absorbed in small

intestines (Wang et al., 2017a).

Overall, from these studies, it can be concluded that curcumin has poor

permeability across intestinal barriers even after dissolution, thus confirming

that the curcumin can be classified as a class IV drug according to

310   biochemical classification scheme (poorly soluble and poorly permeable).

3.3. High metabolism rate of curcumin

Curcumin delivered orally undergoes extensive metabolic reduction and

conjugation, which result in poor bioavailability (Garcea et al., 2004). The

315   mechanisms of curcumin metabolism are shown in **Figures 3 and 4**.

The Phase I metabolism includes the reduction of the four double bonds

of the heptadiene-3, 5-dione structure of curcumin. The reduced curcumin

metabolites dihydrocurcumin, tetrahydrocurcumin, and hexahydrocurcumin

were detected in plasma (rats and humans) following curcumin oral

320   supplementation. The reduction processes were catalysed by NADPH-

dependent curcumin reductases that exist in the liver (Hoehle et al., 2007;

Ireson et al., 2001). E. coli, the microorganism that commonly exists in small

intestine and colon, was found to have the ability to catalyse the metabolic

reduction processes of curcumin (Hassaninasab et al., 2011).

During the Phase II metabolism, glucuronidation and sulfation of curcumin and the reduced metabolites take place. The conjugation activities are catalysed by UDP-glucuronosyltransferases and sulfotransferase respectively (Ireson et al., 2002). The conjugated metabolites include curcumin sulfate, curcumin glucuronide sulfate, curcumin glucuronide, dihydro curcumin glucuronide, tetrahydro curcumin glucuronide and hexahydro curcumin glucuronide. *In vivo* studies in rats and humans showed that the curcumin glucuronide and curcumin glucuronide/sulfate conjugates were found in the plasma, jejunum and livers (Asai and Miyazawa, 2000, Hoehle et al.,2007, Ireson et al., 2001, 2002). An *in vivo* study conducted in rats showed that the UDP-glucuronosyltransferases and sulfotransferase enzymes activities were found in livers, kidneys, small intestine mucosa and colon intestinal mucosa. No conjugated enzyme activities were found in the plasma (Asai and Miyazawa, 2000). These observations might indicate that the conjugated curcumin metabolites are probably produced in these tissues before present in the plasma circulation. The glucuronidation activity was found to occur more extensively in human intestines than in rats, while it became less extensive in human liver than in rats. The difference of metabolism extension may be due to the differences in conjugation-hydrolysing enzymes content in intestines & livers of humans and rats (Hoehle et al.,2007, Ireson et al., 2001, 2002).

3.4. Chemical stability of curcumin

Like its aqueous solubility, the chemical stability of curcumin in aqueous solution is affected by change in pH. Curcumin is most stable at pH 1–6, when in the environment of stomach or small intestine. However, the aqueous solubility becomes extremely poor at this pH range while the stability of curcumin decreases significantly when the pH is above 7 (Esatbeyoglu et al., 2012, Wang et al., 1997). In a stability test, using 5 mM curcumin solution (dissolved in methanol and added to 0.1 M phosphate buffer solution at pH 7.2) incubated at 37°C for different lengths of time and analysed by HPLC, the results showed that 90% of the curcumin was degraded within 30 min to various degradation products including vanillin, ferulic acid and feruloyl methane (**Figure 5**). Vanillin was identified to be the major degradation product in this assay following first-order kinetics (Wang et al., 1997). Overall, the stability problem of curcumin really affects the oral bioavailability since curcumin can be rapidly degraded at alkaline solutions and is poorly soluble in acidic aqueous solutions (even though more stable).

4. Novel formulations developed for improving curcumin's oral bioavailability

Numerous efforts have been made to find a way to overcome the low oral bioavailability of curcumin and a great number of novel formulations have been developed by researchers to achieve this goal. Details of recent

17

developments in curcumin formulations are discussed in the following

370 sections.

4.1. Co-administration of adjuvants

Some adjuvants can decrease the metabolism of curcumin which can help

to improve the bioavailability of curcumin.

375 Piperine (**Figure 6**) is an alkaloid naturally present in black pepper and is

the substance that gives black pepper (Piper nigrum) its pungency. Co-

administration of piperine with curcumin was found to improve the

bioavailability of curcumin (Atal et al., 1985; Shoba et al., 1998). Piperine

inhibits the enzyme UDP-glucuronyltransferase in the liver thereby limiting the

380 extent of curcumin glucuronidation. Because of this process, more curcumin is

available for absorption (Zeng et al., 2017b). An *in vivo* study was conducted

in both rats and humans at an oral dose of 2 g/kg of curcumin with 20mg/kg

piperine, administered simultaneously (Shoba et al, 1998). The relative

bioavailability of curcumin in rats was increased by 1.54-fold while in the

385 human volunteers it increased by 20-fold. However, even though extent of

increase of bioavailability of curcumin was higher in human than in rats, the

amount of curcumin actually being absorbed was in fact higher in rats than in

human (**Figure 7**). In another clinical trial, 2 g of curcumin and 5mg of piperine

were co-administered orally to healthy human volunteers (Anand et al., 2007).

390 The test results revealed that there was an increase of absorption of curcumin

18

by 200%, compared with that of taking curcumin alone (**Figure 8**). Another

study by Zeng et al. (Zeng et al., 2017b) investigated the effect of pre-

administration of piperine on the oral bioavailability of curcumin. In this study,

rats received 20 mg/kg piperine initially followed by curcumin (200 mg/kg) at

395   various time intervals between 0.5-8 h after piperine administration. The rats

that received pre-administration of piperine before the curcumin all showed

remarkable enhancement in curcumin oral bioavailability, especially at 6 hours

after taking piperine with AUC_{0-t} increased 97-fold when compared to pure

curcumin. In contrast, rats that received the same oral dose of piperine and

400   curcumin at the same time exhibited much lower enhancement in AUC_{0-t}, by

1.67-fold relative to pure curcumin (**Figure 9**). It was also found that that

piperine causes time-dependent and selective suppression of UDP-

glucuronyltransferase and sulfotransferases, which reducing curcumin

metabolism (Volak et al., 2008; Zeng et al., 2017b).

405   Apart from piperine, several other natural compounds such as silibinin, and

quercetin have been shown to inhibit the effects oF UDP-

glucuronyltransferase (Grancharov et al., 2001; Williams et al, 2002).

Quercetin is a plant flavonol that is present in many fruits, vegetables and

grains (Lund and Pantuso, 2014). Silibinin is a flavonoid that extracted from

410   the medicinal plant Silybum marianum (milk thistle) (Cheung et al., 2010). The

effect of co-delivering natural curcumin metabolism enzyme inhibitors on the

oral bioavailability of curcumin was studied using a self-emulsion formulation

of curcumin. The self-emulsion formulation (containing 100 mg/kg curcumin) was delivered orally to mice with or without either piperine (125 mg/kg),

415 quercetin (100 mg/kg), or silibinin (100 mg/kg). The pharmacokinetic results showed that piperine co-administration showed the highest C_{max} of curcumin. However, curcumin concentration in the plasma was highly variable (0–2.4 µM curcumin plasma levels), which was deemed unacceptable. Co-administration of quercetin or silibinin showed much more stable plasma levels of curcumin

420 and both increased the average C_{max} of curcumin. Silibinin co-delivery resulted in higher C_{max} of curcumin than quercetin so the bioavailability study was only conducted for silibinin. The results reported that co-administration of silibinin improved the overall bioavailability of curcumin by approximately 3.5-fold (AUC_{0-6} 0.2613 ± 0.0368 Vs. 0.0808±0.0469 h·µmol/L for SMEDDS

425 without adjuvant co-delivery) (Grill et al.,2014).

An *in vitro* Caco-2 cell monolayers permeability study examined how oral co-administration of piperine, quercetin or resveratrol can affect the intestinal absorption of curcumin. Resveratrol (trans-3,5,4′-trihydroxystilbene), is a natural plant compound that is present in grapes, berries and other plants. All

430 the three compounds showed an increase in curcumin permeability across the Caco-2 cell monolayers. Quercetin and resveratrol increased the curcumin permeability by 1.46-fold and 1.25-fold, respectively. The highest effect on curcumin permeability was from piperine, which increased the permeability by 2.33-fold. Interestingly, when quercetin and resveratrol were combined

435 together with curcumin, the permeability increased by 1.85-fold. This indicated

that there is an additive effect of resveratrol and quercetin on curcumin

absorption (Lund and Pantuso, 2014)

Co-delivery of natural compounds like piperine, quercetin, resveratrol and

silibinin decreased the metabolism of curcumin which eventually increased the

440 absorption of curcumin. It is a promising and easy way to improve the oral

bioavailability of curcumin and could be investigated further in the

development of novel drug delivery systems.

4.2. Nanoparticles

445 Nanoparticle-based delivery system is another effective strategy to

improve the oral bioavailability of poorly water-soluble drugs. The nano-size of

the particle (10–1000 nm) leads to a greater surface area for the drug

particles thereby increasing the area of physical interaction with the solvent.

According to Noyes-Whitney equation, the dissolution rate is directly

450 proportional to the surface area. Therefore, nano-sized drug particles with

higher surface area are likely to be dissolved more rapidly. Furthermore,

reducing the drug particle size to nanometer size, according to the Ostwald-

Freundlich equation, can increase the saturation solubility of the drug.

(Jahagirdar et al., 2018; Merisko-Liversidge et al., 2003; Müller et al.,2011).

455 A list of approved nanodrugs is shown at Table 1. In comparison with the

conventional formulations, these nanodrugs benefited from increased

dissolution rate and saturation solubility, which leads to higher bioavailability

(Junghanns and Muller, 2008).

460   Table 1. A List of FDA approved nanodrugs (Junghanns and Muller, 2008).

Trade name	Generic name	Route of administration	Indication
Emend®	Aprepitant as nanocrystal	Oral	Preventing nausea and vomiting
Megace ES®	Megestrol acetate as nanocrystal	Oral	Treating loss of appetite and wasting syndrome in people with acquired immunodeficiency syndrome (AIDS).
Rapamune®	Rapamycin (sirolimus) as nanocrystals formulated in tablets	Oral	Immunosuppressant
Tricor®	Fenofibrate as nanocrystals	Oral	Treating hypercholesterolemia and hypertriglyceridemia
Triglide®	Fenofibrate as nanocrystals	Oral	Treating hypercholesterolemia and hypertriglyceridemia

*Compared with the conventional formulations

Nanoparticle technology is widely used for delivering poorly-water soluble

drugs or substances (Bisht et al., 2007; Ensign et al., 2012; Singh and Lillard,

465   2009; Zhang et al., 2008;). A curcumin loaded lipopolysaccharide

nanoparticles (C-LPNCs) was developed to improve the oral bioavailability of

curcumin (Chaurasia et al., 2015). Soluthin® MD, a phosphatidylcholine-maltodextrin based hydrophilic lipopolysaccharide, was used as the nanocarrier to load curcumin. Poloxamer 188 was added as a stabiliser to

470 prevent aggregation and size growth of the C-LPNCs. A graphical scheme of this formulation is shown in **Figure. 10**. Burst dissolution of the curcumin was observed in the first 30 min at pH 7.4 buffer solution, which was due to the amorphous distribution of the curcumin particles in the C-LPNCs. Subsequently the dissolution rate was reported to gradually reduce and

475 became relatively stable after 12 hours. After 24 hours, 80% of the curcumin in the C-LPNCs dissolved in the solution. The C-LPNCs were evaluated *in vivo* to investigate its effect on the oral bioavailability. A curcumin equivalent dose of 50mg/kg was administrated orally to Albino Wister rats. The C_{max} and AUC_{0-t} of curcumin was found to have increased by 104.8-fold and 55.2-fold

480 respectively when administrated as the C-LPNCs, compared with the unformulated curcumin. Lymphatic transport was found to be involved in the oral absorption of C-LPNCs, which can reduce curcumin hepatic metabolism in liver thus contributing to the increase in curcumin bioavailability. In addition, maltodextrin in the formulation can protect curcumin from degradation in the

485 harsh environment of the gastrointestinal tract, which could be another reason for the improvement of the oral bioavailability. Anticancer activity of C-LPNCs against colon cancer was investigated *in vivo* in colon-26 tumour bearing rats. A curcumin equivalent dose of 50 mg/kg was delivered orally daily to the rats

for 30 days. At the end of the study, 100% survival rate was observed in the

490　group being treated with the C-LPNCs while 33.33% survival rate was

observed in the group receiving pure curcumin (Chaurasia et al., 2015).

In another study, a simple method called CO_2-assisted in situ nano-

amorphization was used to prepare curcumin-lipopolysaccharide based oral

nanosuspension to improve the bioavailability and anticancer efficacy of

495　curcumin (Wang et al., 2017b). In this method, curcumin, citric acid and a

stabilizer, Brij78, were first dissolved in ethanol. The solvent was then

removed via evaporation, resulting in the formation of a solid mixture.

Subsequently carbonated solution was added to the solid mixture to form the

curcumin loaded nanosuspension. In an *in vivo* test in rats, it was reported

500　that the oral bioavailability of curcumin had improved by 3.70-fold from the

CUR/Brij78 nanosuspensions compared with that of free curcumin

suspension.

Another novel curcumin-loaded nanoparticle was developed by using an

ionotropic gelation method. Alginate and polysorbate combinations were used

505　to form the nanoparticles to entrap curcumin (Govindaraju et al., 2019). This

formulation showed low release of curcumin in gastric and intestinal

environments but a sustained release within the colon. This phenomenon was

due to colonic microflora, which helped to digest the alginate thus allowing

curcumin to be released from the nanoparticles. In the human body, at a

510　curcumin dose of 100 mg, the nanoparticle formulation increased the oral

bioavailability of curcumin by 5-fold than that of free curcumin suspension. Since most of the curcumin was released and absorbed in the colon, this formulation might be a promising approach for oral delivery of curcumin for targeting colonic diseases.

515   Applying coating to the surface of nanoparticles may help to prevent agglomeration to occur. Commonly used polymers for such coating are polyethylene glycol (PEG), poly(vinylpyrrolidone) (PVP), dextran, chitosan, pullulan etc. Surfactants like sodium oleate and dodecylamine have also been used for nanoparticle coating (De Jong and Borm, 2008). In another study, a

520   curcumin-loaded solid lipid nanoparticles (SLNs) with N-carboxymethyl chitosan (NCC) coating was prepared through a modified hot homogenization and sonication method (Baek and Cho, 2017). The NCC coated SLN samples exhibited 9.5-fold higher oral bioavailability than that of curcumin solution. Inhibition of burst release (over-rapid release) of curcumin was observed in

525   NCC coated SLNs in simulated gastric fluid (pH1.2) thus indicating that NCC coating was able to address the burst release problem that SLNs usually have in an acidic environment.

       Among the nanoparticle formulations mentioned above, the nanosuspension prepared by CO_2 assisted in situ nano-amorphization method

530   (Wang et al., 2017b) exhibited the highest curcumin oral bioavailability with the AUC_{0-t} value of 365.73 μg·h/ml in rats. A comparison of the curcumin oral absorption data between each nanoparticle formulation is shown in **Figure.**

11.

4.3. Liposomes

Liposomes are a type of drug delivery system which contain a

phospholipid bilayer structure giving them an ability to encapsulate both

hydrophilic and hydrophobic substances (Anand et al., 2007). As a drug

delivery approach, liposomes have the advantage of being biodegradable,

540 nontoxic, and remarkably biocompatible (Li et al., 2018).

A hybrid liposomal formulation that consisted of chitosan and soybean

lectithin was developed as a drug vehicle for curcumin (Peng et al., 2017).

Bioavailability of curcumin from the liposomal formulation was testing using

caco-2 cells. The hybrid liposomes exhibited higher cellular uptake rate than

545 that of phospholipid liposome, 1.66-fold higher at 0.5 hours after incubation

and 1.256-fold higher after 4 hours incubation. The researchers reported a

sustained release of curcumin, increased positive charge and decreased

hydrophobicity from the hybrid liposomal formulation were the main reasons

for the increased curcumin bioavailability.

550 In another study, a liposomal formulation coated with chitosan was tested

in simulated gastric fluid (pH between 2 and 3) and in simulated intestinal fluid

(pH 7). It was reported that around 80% of the curcumin loaded in the

liposome dissolved in the simulated gastric and the simulated intestinal fluids

(Cuomo et al., 2018).

555　　　In the research area of curcumin liposomal formulation, the current trend is

to use hybrid liposomal formulations to help to improve the bioavailability of

curcumin. The studies mentioned above showed that the hybrid liposomal

formulations have better performance in improving bioavailability of curcumin

than the conventional curcumin-loaded liposomes and the unformulated

560　　curcumin.

4.4. Micelles and polymer micelles.

Micelles are spherical aggregates of surfactants that form spontaneously

when the surfactants reach a critical micelle concentration (CMC) at a certain

565　　temperature in aqueous solution (Xu et al.,2013). The size of micelles

normally range between 20 to 80 nm. Typical micelles are comprised of an

outer shell formed by hydrophilic head groups and a core formed by

hydrophobic tail groups. Micelles can be used as vesicles to load and deliver

poorly water-soluble drugs. The hydrophobic core can encapsulate the

570　　lipophilic drugs and the hydrophilic outer shell to protect the drugs from being

inactivated in the gastrointestinal environment. As a result, solubilization and

stability of the drugs are improved (Haley and Frenkel, 2008).

A novel curcumin-loaded mixed micelle (CUR-MM) that consist of two

surfactants (Pluronic F-127 and Gelucire® 44/14) was developed (Patil et al.,

575　　2015). The formulation showed that it can enhance the oral bioavailability of

curcumin and its anti-cancer effect. The optimised CUR-MM formulation with

size of 188 ± 3 nm and an entrapment efficiency of 76.45 ± 1.18% w/w

exhibited significant enhancement in the oral bioavailability of curcumin (by

approximately 55-fold) and cytotoxicity to human lung cancer cell line A549

(by approximately 300%), in comparison with free curcumin. The improved

oral bioavailability and anti-cancer effects of curcumin was attributed to the

controlled release of curcumin from the CUR-MM, increase of curcumin

solubility from micellization and inhibition of P-glycoprotein by the surfactants.

In another study, a sophorolipid nano-micelle formulation was prepared by

using a 'pH-driven method' (Peng et al., 2018). *In vivo* test results showed that

it increased curcumin's oral bioavailability by 3.6-fold compared with the

unformulated curcumin. This proves that biosurfactants like sophorolipid,

obtained from natural sources, could be used for formulating drug delivery

systems to enhance the oral bioavailability of curcumin. The preparation

method used in this study, the pH-driven method, does not require heat and

organic solvents, thus making it a simple and cost-effective way for producing

nano-sized curcumin products.

A clinical trial was conducted among 23 healthy human candidates (13

male and 10 female) to assess a micellar curcumin formulation that composed

of micronised curcumin powder and Tween-80 (Schiborr et al., 2014). The

result of pharmacokinetics studies showed that the ingestion of a single oral

dose of 500 mg micelle encapsulated curcumin (equivalent to 410 mg

curcumin) resulted in a C_{max} of 3.228 µmol/L compared to 0.007 µmol/L of free

curcumin powder. Both male and female subjects have almost the same T_{max},

600   but the female subjects exhibited higher C_{max} of 3.701 μmol/L in comparison

with 2.612 μmol/L for male subjects, indicating that women might be

absorbing more curcumin than men in this study.

A novel self-assembled, curcumin-loaded polymeric micelle was developed

for improving curcumin oral absorption (Wang et al.,2015). It consisted of di-

605   tocopherol polyethylene glycol 2000 succinate (TPGS2 K), octadecanoic acid,

12-hydroxy-, polymer with alpha-hydro-omega-hydroxypoly (oxy-1,2-

ethanediyl) and Pluronic F127. Both in vitro and in vivo test results revealed

that the micelle system provided a better intestinal absorption of curcumin

than free curcumin. Oral administration of the micelle formulation in rats

610   resulted in higher AUC_{0-t} of curcumin (870.2±466.78 mg·h/L) compared with

the standard curcumin (AUC_{0-t} of 303.58±294.31 mg·h/L). Furthermore,

lymphatic transport pathways were found to be involved in the absorption of

the micelle system, which helps curcumin to avoid first-pass metabolism.

Overall, a major increase in oral bioavailability of curcumin was

615   demonstrated in the recently developed novel micelles formulations. These

results indicate that micelles are a promising way for delivering curcumin

orally and worthy of further studies in the future. A comparison plot to describe

the results of curcumin oral bioavailability from different micellar formulations

is shown in **Figure. 12**.

620

4.5. Curcumin-loaded nano and micro-emulsions

Nanoemulsions, also known as submicron emulsions, is another type of nano-sized drug delivery system. They are single phase, isotropic

625 thermodynamically stable systems that consist of emulsified oil, water and amphiphilic molecules (surfactants). The size of the emulsion droplets typically range between approximately 10–1000 nm (Gurpreet and Singh, 2018). A Thiol modified chitosan coated, curcumin-piperine loaded oil-in-water nanoemulsion was developed (Vecchione et al., 2016). The optimised

630 formulation has nano-droplets size of 110nm, weight ratio of curcumin: piperine in 100 to 1 and chitosan thiolation level of 14–15%. At an oral dose equivalent to 8mg/kg of curcumin, the AUC_{0-t} value of curcumin increased by 64-fold (343.3 µg·h/ml) than that of standard curcumin (5.4 µg·h/ml). Comparing with the two piperine strategies that were reviewed in section 3.1

635 (Shoba et al, 1998; Zeng et al., 2017b), the optimised curcumin-piperine loaded nanoemulsion formulation is 94-fold and 1505-fold higher in terms of the AUC_{0-t} values. This indicates that the combination of piperine with the nanoemulsion technology is much more effective than only using piperine alone in improving the oral bioavailability of curcumin. In another study, a

640 novel lipid nanoemulsion containing curcumin (CNELNs) was prepared and tested for changes in bioavailability in *in vitro* and *in vivo* models (Wan et al., 2016). The mean absorption constants (K_a) and effective permeabilities (P_{eff})

over the whole intestine system were increased by 2.98-fold and 6.65-fold, respectively. The relative bioavailability of CNELNs to standard curcumin was

645 733.59%, which was possible due to the increase of intestinal absorption. CNELNs also displayed stronger effect in suppressing the growth of human lung cancer cell A549. A curcumin-phospholipid complex was incorporated into a self-nanoemulsion system consisting of castor oil, Tween 80 and PEG 400 (Shukla et al., 2016). The combined formulation showed significant higher

650 serum concentration of curcumin than free curcumin and curcumin-phospholipid complex. Using an oral dose of 100 mg/kg in rats, the C_{max} of curcumin from the combined formulation was 487.7 ± 53.4ng/ml, compared to 21.6 ± 3.6 ng/ml for free curcumin and 54.6 ± 3.7 ng/ml for curcumin-phospholipid complex. The relative bioavailability of curcumin from the

655 combined formulation was 7.67-fold and 52.55-fold higher than that of curcumin-phospholipid complex and unformulated curcumin. Several research studies have been carried out to study the potential for using nanoemulsion strategy to improve the oral bioavailability of curcumin. The results of these studies demonstrated that it is a promising strategy to fulfil the goal of

660 improving curcumin's oral bioavailability. Among the nanoemulsion formulations reviewed, piperine loaded in an oil-in water nanoemulsion with modified chitosan coating (Vecchione et al., 2016) showed the highest curcumin oral absorption with the AUC_{0-t} value of 343.8μg·h/ml. In contrast, the other two nanoemulsion formulations (Shukla et al., 2016; Wan et al.,

665 2016) have much poorer curcumin bioavailability with AUC_{0-t} value of

0.7μg·h/ml and 2.97μg·h/ml (**Figure 13**).

Microemulsion is an isotropic colloidal system of micron-sized droplets that

consists of water, oil, surfactant and cosurfactants. When in a microemulsion

system, drug compounds can be entrapped within the oil droplets, which

670 protect them from both enzymatic and chemical degradations thus increasing

the residence time and bioavailability of the drugs (Constantinides, 1995).

Interestingly, the droplet size of microemulsion is not in micrometre but

between 10 to 100 nm. Microemulsion is fairly similar to nanoemulsion in

terms of the structure. What differentiating it from nanoemulsion is that

675 microemulsion is thermodynamically stable whereas nanoemulsion is not.

Also, microemulsion normally have a narrow particle size distribution

compared to nanoemulsions (McClements, 2012). A self-emulsifying

microemulsion drug delivery system (SMEDDS) was developed to improve

the oral bioavailability of curcumin (Dhumal et al., 2015). A semi-synthetic

680 bicephalous heterolipid known as E1E was used in this formulation, along with

Solutol HS15 (a surfactant) and Transcutol HP (a cosurfactant) to form the

microemulsion encapsulating curcumin. An optimised SMEDDS formulation

with drug loading efficiency of 70.52 ± 2.46 mg/g was orally administrated to

rats at a curcumin dose of 50 mg/kg. Plasma analysis showed that the C_{max}

685 and AUC_{0-t} of curcumin from the SMEDDS were 4.921± 0.42(μg/mL) and

17.30 ± 1.50 (μg.h/ml) respectively, in comparison with free curcumin

suspension with 0.186 ± 0.006 (µg/ml) and 0.234 ± 0.023(µg.h/ml)

respectively. T_{max} remained unchanged in both SMEDDS and the free

curcumin suspension 60 min after oral administration. In another study, a self-

microemulsifying curcumin (SME-Cur) entrapped in a hydroxypropylmethyl

cellulose (HPMC)-based sponge was developed to study oral absorption of

curcumin (Petchsomrit et al., 2015). The *in vivo* study was performed in

rabbits at a curcumin equivalent oral dose of 12.5 mg/kg. The HPMC sponge

entrapped SME-Cur showed significantly higher C_{max} and AUC_{0-t} (1.77 ± 0.13

mg/ml and 2615.68 ± 97.79 ng/h/ml, respectively) than unformulated curcumin

at dose of 50 mg/kg (0.30 ± 0.03 mg/ml and 509.49 ± 47.77ng h/ml,

respectively). The *in vitro* drug release test found that the HPMC-based

sponges entrapped SME-Cur provided a sustained release of curcumin and

led to a higher percentage release compared with the unwrapped SME-Cur

and free curcumin. The improved drug release could be attributed to the drug-

polymer interaction leads to the inhibition of precipitation and crystallization of

curcumin in solution.

Compared to nanoemulsions, microemulsions have received less attention

since there were only a few studies on their use in improving the oral

bioavailability of curcumin (**Figure 14**). However, the studies of

microemulsions reviewed in this article both showed considerable

improvement in curcumin's oral bioavailability (Dhumal et al., 2015;

Petchsomrit et al., 2015). All of these indicate that microemulsions are still a

33

potent and promising technology to overcome curcumin's oral delivery

710 problems and it is worthy of further studies in the future.

4.6. Solid dispersion

By definition, a solid dispersion is a solid product where at least one drug

is entrapped in a hydrophilic polymeric carrier and the drug(s) is/are

715 molecularly dispersed in the polymeric carrier (Chiou and Riegelman, 1971).

The principle of solid dispersion to improve the drug bioavailability was to first

rapidly release the drug particles from the polymeric carrier to create a

supersaturated solution after which the concentration is maintained long

enough for the drug to be absorbed (Craig, 2002; Kumar and Gupta, 2013;

720 Vasconcelos et al.,2007). Drugs in supersaturation state tend to precipitate

rapidly before the absorption to take place which results in reduced

bioavailability. Fortunately, the polymer excipients that are commonly used for

preparing solid dispersion also have the ability to inhibit drug precipitation and

prolong the supersaturation, such as hydroxypropylmethyl cellulose (HPMC),

725 hydroxypropylmethyl cellulose acetate succinate (HPMC-AS) and vinyl

polymers such as poly (vinylpyrrolidone) (PVP). The mechanism of how

polymers prolong drug supersaturation is still not fully understood.

Nevertheless, it is generally believed to be as a result of hydrogen bond

formation between the polymers and the drugs, based on the observation that

730 polymers are effective in inhibiting precipitation of drugs rich in hydrogen-bond

acceptors (Bevernage et al., 2011; Gao et al., 2009; Miller et al., 2008). Solid

dispersion continues to be a widely studied strategy to improve oral

bioavailability of poorly water-soluble drug candidates (Chuah et al., 2014;

Onoue et al., 2010; Seo et al., 2012). A list of FDA approved solid dispersion

735   drugs is shown at Table 2.

Table 2: A list of FDA approved solid dispersion drugs (Baghel et al.,2016)

Trading name	Active ingredient	Carrier	Preparation method	Dosage form
Kalydeco®	Ivacaftor	HPMCAS	Spray drying	Tablet
Zelboraf®	Vemurafenib	HPMCAS	Coprecipitation	Tablet
Incivek®	Telaprevir	HPMCAS	Spray drying	Tablet
Intelence®	Etravirine	HPMC	Spray drying	Tablet
Novir®	Ritonavir	PVP/PA	Melt extrusion	Tablet
Kaletra®	Lopinavir	PVP/PA	Melt extrusion	Tablet

A recent study combined solid dispersion strategy with nanotechnology

740   and developed a novel self-nanomicellizing solid dispersion (NCF) for

delivering curcumin orally (Parikh et al., 2018a). Soluplus® (polyvinyl

caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was used

as a carrier for curcumin in the NCF formulation. NCF exhibited significant

increase in aqueous solubility of curcumin (over 20,000-fold higher than the

745 curcumin control). Considerable improvement in dissolution rate and small-

intestinal permeability of curcumin were also found with the NCF formulation.

Furthermore, improved curcumin stability in alkaline environment was found.

As a result of the increased dissolution, solubility, permeability and alkaline

solution stability, the oral bioavailability of curcumin from the NCF was

750 significantly enhanced by 117-fold compared with pure curcumin.

In another study, an amorphous curcumin solid dispersion was prepared

with disodium glycyrrhizin (Na_2GA) via ball milling (Zhang et al., 2018). Na_2GA

was able to form micelles when dissolved in water and encapsulate the

amorphous curcumin particles. *In vivo* evaluation showed that the self-micelle

755 forming solid dispersion provided a 19-fold increase in curcumin oral

bioavailability over free curcumin. In addition, the solid dispersion formulation

improved curcumin permeability across the gastrointestinal membranes.

A curcumin-loaded ternary solid dispersion system was prepared by using

mannitol as the hydrophilic carrier and d-α-Tocopheryl polyethylene glycol

760 1000 succinate (vitamin E TPGs) as the surfactant (Song at al., 2016). TPGs

was selected due to its safety and potential to inhibit P-glycoprotein efflux.

The aqueous solubility of curcumin from the solid dispersion formulation

remained stable across a pH range from 1.2 to 7.4, which diminished the pH-

dependent solubility pattern in pure curcumin powder. Pharmacokinetics

765 studies revealed that the C_{max} and AUC_{0-t} of curcumin were increased by 86-

and 65-fold respectively, in comparison with pure curcumin powder. The solid

36

dispersion formulation also exhibited an inhibition effect on P-glycoprotein. and this was believed to be the main reason for the increased curcumin intestinal absorption observed from the solid dispersion system.

770   A curcumin-loaded solid dispersion formulation was developed by using Gelucire 50/13 (a non-ionic water-dispersible surfactant) as the carrier material (Teixeira et al., 2015). The solid dispersion formulation was prepared by spray drying. The aqueous solubility of curcumin was significantly increased by the solid dispersion (2700 µg/ml), which was 3600-fold higher

775   than the unformulated curcumin (0.75 µg/ml). The solid dispersion demonstrated rapid release of curcumin at 10 min, with 90% and 73% of curcumin being released at pH 1.2 and 7.4, respectively. The percentage of curcumin released was also considerably higher than pure curcumin. Results from rat plasma sample analysis indicated a 5.5-fold increase of curcumin

780   plasma concentration from the solid dispersion compared with the unformulated curcumin under the same oral dose (500mg/kg). Since spray drying is a technique that is suitable for scaled-up production, solid dispersion formulation developed in this study could be a promising way to improve curcumin bioavailability from an industrial perspective.

785   In another study, an excipient-free co-amorphous curcumin-piperine solid dispersion (co-amorphous CUR-PIP) was prepared by a melting and quench cooling method (Wang et al., 2019). This formulation has a combined solid dispersion effect of increasing drug dissolution along with piperine's effect of

inhibiting the glucuronidation of curcumin *in vivo*. In this study, higher

790   dissolution rate and longer-lasting supersaturated curcumin concentration

were observed from the co-amorphous CUR-PIP. This could be due to

piperine's effects to suppress UDP-glucuronyltransferase and

sulfotransferases in the intestines and liver (Zeng et al., 2017b). In addition,

the permeability of curcumin across the gastrointestinal membrane was

795   elevated by 2.67-fold compared with pure curcumin, which was linked to

piperine's ability to inhibit curcumin glucuronosyltransferases. As a result of

faster, longer-lasting supersaturation dissolution and higher GI permeability,

the oral bioavailability of curcumin was enhanced by 2.16- and 1.92-fold with

the co-amorphous CUR-PIP relative to the crystalline and amorphous

800   curcumin. Comparing with the previously mentioned strategies that used

piperine for curcumin, the co-amorphous CUR-PIP showed around 8-fold and

134-fold higher AUC_{0-t} values than the curcumin-piperine co-administration

strategy (Shoba et al, 1998) and the pre-treatment of piperine strategy (Zeng

et al., 2017b). However, it is around 11-fold lower compared to the curcumin-

805   piperine loaded nanoemulsion (Vecchione et al., 2016). A comparative graph

between the solid dispersion formulation and the nanoemulsion formulation is

shown in **Figure. 15**.

The results from the studies mentioned above suggest that solubility and

dissolution of curcumin can be greatly improved by solid dispersion strategies,

810   thus leading to improvement in curcumin's oral bioavailability. The selection of

carriers and surfactants also play a vital role in the performance of solid

dispersion formulations in improving oral bioavailability of curcumin.

Among all the solid dispersion formulations reviewed in this article, the

self-nanomicellising solid dispersion prepared using Soluplus (Parikh et al.,

815   2018a) exhibited significantly higher curcumin oral absorption compared with

the other solid dispersion formulations. A comparative graph is shown in

Figure. 16.

5. Conclusions

820   Decades of studies have proved that curcumin can be well-tolerated in

human bodies, with numerous therapeutic potentials. However, despite

curcumin's pharmacological efficacy and safety, it is still not licenced as a

valid therapeutic agent mainly due to the very poor oral bioavailability of

curcumin. As discussed earlier in this article, the main factors that contribute

825   to the poor oral bioavailability of curcumin are low aqueous solubility, poor

intestinal permeability, chemical stability, rapid metabolism and elimination.

A range of novel formulations have been developed in recent years and

many of them have demonstrated considerable improvement in the oral

bioavailability of curcumin. A summary of these novel developments is given in

830   Table 3. The curcumin oral absorption results of the formulation with obvious

increase in curcumin bioavailability are summarised and compared in **Figure

17**. From this data it can be summarised that the self-nanomicellizing solid

dispersion (NCF) prepared by Soluplus showed the highest curcumin oral bioavailability with the AUC_{0-t} value of 1998.6 ± 361.5μg·h/ml at a curcumin

835 equivalent dose of 47mg/kg in rats (Parikh et al., 2018a). This shows the great potential of solid dispersion strategy for the application in improving curcumin absorption via oral administration. Whether improvement of oral bioavailability of curcumin can improve the therapeutic efficacy of the compound needs to be evaluated. A follow-up study was carried out to evaluate the efficacy of

840 NCF against Alzheimer's disease in *in vitro* (SHSY5Y695 APP human neuroblastoma cell line with induced toxicity) and *in vivo* (transgenic mice with Alzheimer's diseases) models. In the *in vitro* model, NCF (equivalent to 10 μg/mL of curcumin) displayed better efficacy than CUR control (10 μg/mL) against cytotoxicity which induced by $CuSO_4$, H_2O_2 and Aβ42. This indicated

845 that NCF has better neuroprotective effect than the unformulated curcumin. As for the *in vivo* study, NCF, curcumin control and donepezil (a medication used for treating Alzheimer's diseases) were orally administrated to mice in order to investigate their long-term (3 months) efficacy against Alzheimer's diseases. The efficacy was evaluated by behavioural tests of the mice and the results

850 showed that the NCF has significantly better efficacy to repair the cognitive functions and behaviour of mice than the curcumin control and even donepezil. Also, it has been reported that it prevents any further deterioration in the behaviour of mice. During the *in vivo* study, the formulation was well-tolerated with no obvious toxicity. This makes NCF a safe and effective option

855 for the treatment of Alzheimer's diseases. It also proved that the improvement

of the oral bioavailability of curcumin could lead to good therapeutic effect

(Parikh et al. 2018b).

However, it is difficult to directly compare each formulation because of the

differences in administered dose, experimental designs, and methods of

860 analysis. No cross-over studies have been conducted for the novel curcumin

formulations mentioned in this article. It is suggested that in order to design

standardised controlled trials for different curcumin formulations in the future,

it is imperative to understand and verify which formulation is the best in terms

of oral bioavailability and therapeutic effect.

865 In summary, curcumin has been demonstrated to have a wide range of

therapeutic effects. However, due to its physical properties it is seriously

lacking in aqueous solubility, which has been related to its poor bioavailability.

Advances in the development of novel formulations should assist in improving

bioavailability, which can then be related to categorically demonstrate

870 curcumin's therapeutic effect in a given condition.

Table 3. A summary of the novel formulations for improving curcumin's oral bioavailability.

Subjects	Amount of curcumin administrated	Formulation	Improved the oral bioavailability of curcumin by	References
Humans	2g	2 g of curcumin + 5mg of piperine was delivered orally simultaneously	2-fold	Anand et al., 2007
Rats	200mg/kg	Pre-administration of 20mg/kg piperine, then 200mg/kg curcumin after 6 hours	97-fold	Zeng et al., 2017b
Albino Wister rats	50mg/kg	Curcumin loaded phosphatidylcholine-maltodextrin based nanoparticles(C-LPNCs)	55.2-fold	Chaurasia et al., 2015
Male SD (Sprague Dawley) rats	50mg/kg	Curcumin loaded nanosuspension, prepared by citric acid and Brij78	3.7-fold	Wang et al., 2017
Humans	100mg	Curcumin loaded, Alginate and polysorbate nanoparticles	5-fold	Govindaraju et al., 2019
Male SD rats	50mg/kg	Curcumin-loaded solid lipid nanoparticles(SLN) with N-carboxymethyl chitosan (NCC) coating	9.5-fold	Baek and Cho, 2017
Caco-2 cells	4µg/mL	Curcumin-loaded hybrid liposomal formulation that consist of chitosan and phospholipid	1.256-fold higher 4h after incubation.	Peng et al., 2017
Male wistar rats	10mg/kg	Curcumin-loaded mixed micelle (consist of Pluronic F-127 and Gelucire® 44/14)	55-fold	Patil et al., 2015
Male SD rats	100 mg/ kg	Curcumin-loaded sophorolipid based nanomicelle	3.6-fold	Peng et al., 2018

Rats	50mg/kg	Self-assembled, polymeric curcumin-loaded micelles, consist of TPGS2 K, HS15 and Pluronic F127	2.87-fold	Wang et al., 2015
Male Wistar albino rats	8mg/kg	Thiol modified chitosan coated, curcumin-piperine loaded, oil-in water nanoemulsion	64-fold	Vecchione et al., 2016
Male SD rats	100mg/kg	Curcumin-loaded self-nanoemulsifying drug delivery system (SNEDDS) , consist of ethyl oleate, tween 80 and PEG 600	1.94-fold	Wan et al., 2016
Rats	100mg/kg	Curcumin-phospholipid complex, entrapped in a self-nanoemulsion that consist of caster oil, Tween 80 and PEG 400	52.55-fold	Shukla et al., 2016
Rats	50mg/kg	Self-emulsifying curcumin loaded microemulsion that consist of E1E, Solutol HS and Transcutol HP	73-fold	Dhumal et al.,2015
Adult male Wistar rats	12.5mg/kg	Self-microemulsifying curcumin (SME-Cur) wrapped in a hydroxyprophylmethyl cellulose (HPMC)-based sponge	5-fold	Petchsomrit et al., 2015
Male SD rats	47 mg/kg	Self-nanomicellizing curcumin-loaded Soluplus solid dispersion	117-fold higher than that of 150mg/kg curcumin suspension	Parikh et al., 2018a
Male S D rats	150mg/kg	Ball milled curcumin loaded, disodium glycyrrhizin (Na2GA) solid dispersion	19-fold	Zhang et al., 2018
Male SD rats	30 mg/kg	Curcumin-loaded ternary solid dispersion system, prepared with Mannitol and TPGs	65-fold higher than 200mg/kg oral dose of pure curcumin	Song et al., 2016
Rats	500mg/kg	Curcumin-Gelucire 50/13 solid dispersion	5.5-fold	Teixeira et al., 2015
Rats	100mg/kg	curcumin-piperine solid dispersion	1.92-fold	Wang et al., 2019

6. References

890 Aggarwal, B., Takada, Y., Oommen, O., 2004. From chemoprevention to chemotherapy: common targets and common goals. Expert Opin. Investig. Drugs. 13(10), 1327-1338. https://doi.org/10.1517/13543784.13.10.1327

Anand, P., Kunnumakkara, A., Newman, R., Aggarwal, B., 2007. Bioavailability of Curcumin: Problems and Promises. Mol. Pharm. 4(6), 807-818.
895 https://doi.org/10.1021/mp700113r

Araiza-Calahorra, A., Akhtar, M., Sarkar, A., 2018. Recent advances in emulsion-based delivery approaches for curcumin: From encapsulation to bioaccessibility. Trends Food Sci. Technol. 71, 155-169. https://doi.org/10.1016/j.tifs.2017.11.009

900 Araujo, M., Antunes, L., Takahashi, C., 2001. Protective effect of thiourea, a hydroxyl-radical scavenger, on curcumin-induced chromosomal aberrations in an in vitro mammalian cell system. Teratog. Carcinog. Mutagen. 21(2), 175-180. https://doi.org/10.1002/1520-6866(2001)21:2%3C175::aid-tcm6%3E3.0.co;2-v

905 Artursson, P., Karlsson, J., 1991. Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. Biochem. Biophys. Res. Commun. 175(3), 880-885. https://doi.org/10.1016/0006-291x(91)91647-u

Asai, A., Miyazawa, T., 2000. Occurrence of orally administered curcuminoid as glucuronide and glucuronide/sulfate conjugates in rat plasma. Life Sci.
910 67(23), 2785-2793. https://doi.org/10.1016/s0024-3205(00)00868-7

Atal, C., Dubey, R., Singh, J., 1985. Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. J. Pharmacol. Exp. Ther. 232(1), 258-262.
915 http://jpet.aspetjournals.org/content/232/1/258.long

Baek, J., Cho, C., 2017. Surface modification of solid lipid nanoparticles for oral delivery of curcumin: Improvement of bioavailability through enhanced cellular uptake, and lymphatic uptake. Eur. J. Pharm. Biopharm. 117, 132-140. https://doi.org/10.1016/j.ejpb.2017.04.013

920 Baghel, S., Cathcart, H., O'Reilly, N., 2016. Polymeric Amorphous Solid Dispersions: A Review of Amorphization, Crystallization, Stabilization, Solid-State Characterization, and Aqueous Solubilization of Biopharmaceutical Classification System Class II Drugs. J. Pharm. Sci. 105(9), 2527-2544. https://doi.org/10.1016/j.xphs.2015.10.008

925   Bernabé-Pineda, M., Ramírez-Silva, M., Romero-Romo, M., González-Vergara, E., Rojas-Hernández, A., 2004. Determination of acidity constants of curcumin in aqueous solution and apparent rate constant of its decomposition. Spectrochim. Acta A Mol. Biomol. Spectrosc. 60(5), 1091-1097. https://doi.org/10.1016/S1386-1425(03)00342-1

930   Bevernage, J., Forier, T., Brouwers, J., Tack, J., Annaert, P., Augustijns, P., 2011. Excipient-mediated supersaturation stabilization in human intestinal fluids. Mol. Pharm. 8, 564–570. https://doi.org/10.1021/mp100377m

Bisht, S., Feldmann, G., Soni, S., Ravi, R., Karikar, C., Maitra, A., Maitra, A., 2007. Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a
935   novel strategy for human cancer therapy. J. Nanobiotechnology. 5(1), 3. https://doi.org/10.1186/1477-3155-5-3

Carolina Alves, R., Perosa Fernandes, R., Fonseca-Santos, B., Damiani Victorelli, F., Chorilli, M., 2018. A Critical Review of the Properties and Analytical Methods for the Determination of Curcumin in Biological and
940   Pharmaceutical Matrices. Crit. Rev. Anal. Chem. 49(2), 138-149. https://doi.org/10.1080/10408347.2018.1489216

Canaparo, R., Finnström, N., Serpe, L., Nordmark, A., Muntoni, E., Eandi, M., Rane, A. and Zara, G., 2007. Expression of CYP3A isoforms and P-glycoprotein in human stomach, jejunum and ileum. Clin. Exp. Pharmacol.
945   Physiol., 34(11), pp.1138-44. https://doi.org/10.1111/j.1440-1681.2007.04691.x

Chang, M.T., Tsai, T.R., Lee, C.Y., Wei, Y.S., Chen, Y.J., Chen, C.R., Tzen, J.T., 2013. Elevating bioavailability of curcumin via encapsulation with a novel formulation of artificial oil bodies. J. Agric. Food Chem. 61(40):9666–9671. https://doi.org/10.1021/jf4019195

950   Chaurasia, S., Patel, R., Chaubey, P., Kumar, N., Khan, G., Mishra, B., 2015. Lipopolysaccharide based oral nanocarriers for the improvement of bioavailability and anticancer efficacy of curcumin. Carbohydr. Polym. 130, 9-17. https://doi.org/10.1016/j.carbpol.2015.04.062

Cheung, C., Gibbons, N., Wayne Johnson, D., Nicol, D., 2010. Silibinin – A
955   Promising New Treatment for Cancer. Anti-Cancer Agents Med. Chem., 10(3), pp.186-195. https://doi.org/10.2174/1871520611009030186

Chiou, W., Riegelman, S., 1971. Pharmaceutical Applications of Solid Dispersion Systems. J. Pharm. Sci. 60(9), 1281-1302. https://doi.org/10.1002/jps.2600600902

960   Chuah, A., Jacob, B., Jie, Z., Ramesh, S., Mandal, S., Puthan, J., Deshpande, P., Vaidyanathan, V., Gelling, R., Patel, G., Das, T., Shreeram, S., 2014.

Enhanced bioavailability and bioefficacy of an amorphous solid dispersion of curcumin. Food Chem. 156, 227-233. https://doi.org/10.1016/j.foodchem.2014.01.108

965 Constantinides, P., 1995. Lipid microemulsion for improving drug dissolution and oral absorption: Physical and biopharmaceutical aspects. Pharm. Res. 12, 1561–72. https://doi.org/10.1023/a:1016268311867

Craig, D., 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 231(2), 131-144.
970 https://doi.org/10.1016/s0378-5173(01)00891-2

Cuomo, F., Cofelice, M., Venditti, F., Ceglie, A., Miguel, M., Lindman, B., Lopez, F., 2018. In-vitro digestion of curcumin loaded chitosan-coated liposomes. Colloids Surf. B Biointerfaces. 168, 29-34. https://doi.org/10.1016/j.colsurfb.2017.11.047

975 De Jong, W.H., Borm, P.J., 2008. Drug delivery and nanoparticles: Applications and hazards. Int. J. Nanomedicine. 3(2), 133-149. https://doi.org/10.2147/ijn.s596

Dhumal, D., Kothari, P., Kalhapure, R., Akamanchi, K., 2015. Self-microemulsifying drug delivery system of curcumin with enhanced solubility
980 and bioavailability using a new semi-synthetic bicephalous heterolipid: in vitro and in vivo evaluation. RSC Advances. 5(110), 90295-90306. https://doi.org/10.1039/C5RA18112G

Dovigo, L.N., Carmello, J.C., de Souza Costa, C.A., Vergani, C.E., Brunetti, I.L., Bagnato, V.S., Pavarina, A.C., 2013. Curcumin-mediated photodynamic
985 inactivation of Candida albicans in a murine model of oral candidiasis. Med Mycol. 51(3). 243–251. https://doi.org/10.3109/13693786.2012.714081

Ensign, L., Cone, R., Hanes, J., 2012. Oral drug delivery with polymeric nanoparticles: The gastrointestinal mucus barriers. Adv. Drug Del. Rev. 64(6), 557-570. https://doi.org/10.1016/j.addr.2011.12.009

990 Esatbeyoglu, T., Hubbe, P., Ernst, I.M.A., Chin, D., Wagner, A.E., Rimbach, G., 2012. Curcumin – from molecule to biological function. Angew. Chem. Int. Ed. Engl. 51(22), 5308-5322. https://doi.org/10.1002/anie.201107724

Gantait, A., Barman, T., Mukherjee, P.K., 2001. Validated method for the estimation of curcumin in turmeric powder. Indian J. Tradit. Know. 10(2), 247-
995 250. http://nopr.niscair.res.in/handle/123456789/11499

Gao, D., Liu, H., Lin, J., Wang, Y., Jiang, Y., 2013. Characterization of drug permeability in Caco-2 monolayers by mass spectrometry on a membrane-based microfluidic device. Lab Chip. 13(5), 978-985.

https://doi.org/10.1039/c2lc41215b

1000 Gao, P., Akrami, A., Alvarez, F., Hu, J., Li, L., Ma, C., Surapaneni, S., 2009. Characterization and optimization of AMG-517 supersaturatable self-emulsifying drug delivery system (S-SEDDS) for improved oral absorption. J. Pharm. Sci. 98, 516–528. https://doi.org/10.1002/jps.21451

Garcea, G., Jones, D., Singh, R., Dennison, A., Farmer, P., Sharma, R.A., 1005 Steward, W.P., Gescher, A.J., Berry, D.P., 2004. Detection of curcumin and its metabolites in hepatic tissue and portal blood of patients following oral administration. Br. J. Cancer. 90(5), 1011-1015. https://doi.org/10.1038/sj.bjc.6601623

Govindaraju, R., Karki, R., Chandrasekharappa, J., Santhanam, M., Shankar, 1010 A.K.K., Joshi, H.K., Divakar, G., 2019. Enhanced water dispersibility of Curcumin Encapsulated in Alginate-Polysorbate 80 Nano Particles and Bioavailability in Healthy Human volunteers. Pharm. Nanotechnol. 7(1), 39-56. https://doi.org/10.2174/2211738507666190122121242

Gurpreet, K. and Singh, S., 2018. Review of Nanoemulsion Formulation and 1015 Characterization Techniques. Indian J. Pharm. Sci. 80(5). 781-789. https://doi.org/10.4172/pharmaceutical-sciences.1000422

Gupta, H., Bhandari, D., Sharma, A., 2009. Recent Trends in Oral Drug Delivery: A Review. Recent Pat. Drug Deliv. Formul. 3(2), 162-173. https://doi.org/10.2174/187221109788452267

1020 Grancharov, K., Naydenova, Z., Lozeva, S., Golovinsky, E., 2001. Natural and synthetic inhibitors of UDP-glucuronosyltransferase. Pharmacol Ther. 89(2), 171–186. https://doi.org/10.1016/S0163-7258(00)00109-1

Grill, A.E., Koniar, B., Panyam, J., 2014. Co-delivery of natural metabolic inhibitors in a self-microemulsifying drug delivery system for improved oral 1025 bioavailability of curcumin. Drug Deliv. Transl. Res. 4(4), 344–352. https://doi.org/10.1007/s13346-014-0199-6

Haley, B., Frenkel, E., 2008. Nanoparticles for drug delivery in cancer treatment. Urol. Oncol. 26, 57–64. https://doi.org/10.1016/j.urolonc.2007.03.015

1030 Hassaninasab, A., Hashimoto, Y., Tomita-Yokotani, K., Kobayashi, M., 2011. Discovery of the curcumin metabolic pathway involving a unique enzyme in an intestinal microorganism. Proc. Natl. Acad. Sci. USA 108(16), 6615-6620. https://doi.org/10.1073/pnas.1016217108

Hatcher, H., Planalp, R., Cho, J., Torti, F., Torti, S., 2008. Curcumin: From 1035 ancient medicine to current clinical trials. Cell. Mol. Life Sci. 65(11), 1631-

1652. https://doi.org/10.1007/s00018-008-7452-4

Hoehle, S., Pfeiffer, E., Metzler, M., 2007. Glucuronidation of curcuminoids by human microsomal and recombinant UDP-glucuronosyltransferases. Mol. Nutr. Food Res. 51(8):932-938. https://doi.org/10.1002/mnfr.200600283

1040   Homayun, B., Lin, X., Choi, H., 2019. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. Pharmaceutics. 11(3), 129. https://doi.org/10.3390/pharmaceutics11030129

Holder, G., Plummer, J., Ryan, A., 1978. The Metabolism and Excretion of Curcumin (1,7-Bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) in
1045   the Rat. Xenobiotica. 8(12), 761-768. https://doi.org/10.3109/00498257809069589

Hong, J., Bose, M., Ju, J., Ryu, J-H., Chen, X., Sang, S., Lee, M-J., Yang, C.S. 2004. Modulation of arachidonic acid metabolism by curcumin and related β-diketone derivatives: Effects on cytosolic phospholipase A 2,
1050   cyclooxygenases and 5-lipoxygenase. Carcinogenesis. 25 (9) 1671–1679. https://doi.org/ 10.1093/carcin/bgh165.

Ireson, C., Orr, S., Jones, D., Verschoyle, R., Lim, C., Luo, J., Howells, L., Plummer, S., Jukes, R., Williams, M., Steward, W., 2001. Characterization of metabolites of the chemopreventive agent curcumin in human and rat
1055   hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. Cancer Res. 61 (3), 1058–1064. https://cancerres.aacrjournals.org/content/61/3/1058

Ireson, C., Jones, D., Orr, S., Coughtrie, M., Boocock, D., Williams, M., Farmer, P.B., Steward, W.P., Gescher, A.J., 2002. Metabolism of the cancer
1060   chemopreventive agent curcumin in human and rat intestine. Cancer Epidemiol. Biomarkers Prev. 11(1), 105-111. https://cebp.aacrjournals.org/content/11/1/105.long

Jahagirdar, P.S., Gupta, P.K., Kulkarni, S.P., Devarajan, P.V., 2018. Polymeric curcumin nanoparticles by a facile in situ method for macrophage targeted
1065   delivery. Bioeng. Transl. Med. 4(1), 141-151. https://doi.org/10.1002/btm2.10112

Jaisamut, P., Wiwattanapatapee, R., Wiwattanawongsa, K., 2013. Influence of Natural Gum on Curcumin Supersaturation in Gastrointestinal Fluids. Int. J. Med. Health Biomed. Bioeng. Pharm. Eng. 7(12), 906-909.
1070   https://doi.org/10.5281/zenodo.1089481

Jantan, I., Bukhari, S., Lajis, N., Abas, F., Wai, L., Jasamai, M., 2011. Effects of -diarylpentanoid analogues of curcumin on chemiluminescence and

chemotactic activities of phagocytes. J. Pharm. Pharmacol. 64(3), 404-412. https://doi.org/10.1111/j.2042-7158.2011.01423.x

1075   Jovanovic, S., Steenken, S., Boone, C., Simic, M., 1999. H-Atom Transfer Is A Preferred Antioxidant Mechanism of Curcumin. J. Am. Chem. Soc. 121(41), 9677-9681. https://doi.org/10.1021/ja991446m

Junghanns, J.U., Muller, R.H., 2008. Nanocrystal technology, drug delivery and clinical applications. Int. J. Nanomedicine. 3(3), 295–309.
1080   https://doi.org/10.2147/IJN.S595

Khan, S., Imran, M., Butt, T.T., Shah, S.W.A., Sohail, M., Malik, A., Das, S., Thu, H.E., Adam, A., Hussain, Z., 2018. Curcumin based nanomedicines as efficient nanoplatform for treatment of cancer: New developments in reversing cancer drug resistance, rapid internalization, and improved anticancer
1085   efficacy. Trends Food Sci. Technol. 80, 8-22. https://doi.org/10.1016/j.tifs.2018.07.026

Kim, M.K., Choi, G.J., Lee, H.S., 2003. Fungicidal property of Curcuma longa L. rhizome-derived curcumin against phytopathogenic fungi in a greenhouse. J. Agric. Food Chem. 51(6), 1578–1581. https://doi.org/10.1021/jf0210369

1090   Khopde, S.M., Priyadarsini, K.I., Venkatesan, P., Rao, M.N., 1999. Free radical scavenging ability and antioxidant efficiency of curcumin and its substituted analogue. Bhiophys. Chem. 80(2), 85-91. https://doi.org/10.1016/s0301-4622(99)00070-8

Klickovic, U., Doberer, D., Gouya, G., Aschauer, S., Weisshaar, S., Storka, A.,
1095   Bilban M., Wolzt, M., 2014. Human Pharmacokinetics of High Dose Oral Curcumin and Its Effect on Heme Oxygenase-1 Expression in Healthy Male Subjects. Biomed. Res. Int. 2014, 1-7. https://doi.org/10.1155/2014/458592

Kumar, S., Gupta, S.K., 2013. Pharmaceutical Solid Dispersion Technology: A Strategy to Improve Dissolution of Poorly Water-Soluble Drugs. Recent Pat.
1100   Drug Deliv. Formul. 7(2), 111-121. https://doi.org/10.2174/18722113113079990009

Kunnumakkara, A.B., Anand, P., Aggarwal, B.B., 2008. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett. 269, 199-
1105   225. https://doi.org/10.1016/j.canlet.2008.03.009

Kurien, B.T., Singh, A., Matsumoto, H., Scofield, R.H., 2007. Improving the Solubility and Pharmacological Efficacy of Curcumin by Heat Treatment. Assay Drug Dev. Technol. 5(4), 567-576. https://doi.org/10.1089/adt.2007.064

Kuttan, R., Bhanumathy, P., Nirmala, K., George M.C., 1985. Potential

anticancer activity of turmeric (Curcuma longa). Cancer Lett. 29 (2), 197–202. https://doi.org/10.1016/0304-3835(85)90159-4

Lao, C., Demierre, M., Sondak, V., 2006a. Targeting events in melanoma carcinogenesis for the prevention of melanoma. Expert Rev. Anticancer Ther. 6(11), 1559-1568. https://doi.org/10.1586/14737140.6.11.1559

Lao, C.D., Ruffin, M.T.4th, Normolle, D., Heath, D.D., Murray, S.I., Bailey, J.M., Boggs, M.E., Crowell, J., Rock, C.L., Brenner, D.E., 2006b. Dose escalation of a curcuminoid formulation. BMC Complement. Altern. Med. 6, 10. https://doi.org/10.1186/1472-6882-6-10

Li, Z.L., Peng, S.F., Chen, X., Zhu, Y.Q., Zou, L.Q., Liu, W., Liu, C.M., 2018. Pluronics modified liposomes for curcumin encapsulation: Sustained release, stability and bioaccessibility. Food Res. Int. 108, 246-253. https://doi.org/10.1016/j.foodres.2018.03.048

Lopez-Jornet, P., Camacho-Alonso, F., Jiménez-Torres, MJ., Orduña-Domingo A, Gómez-Garcia F., 2011. Topical curcumin for the healing of carbon dioxide laser skin wounds in mice. Photomed Laser Surg. 29(12), 809–814. https://doi.org/10.1089/pho.2011.3004

LoTempio, M.M., Veena, M.S., Steele, H.L., Ramamurthy, B., Ramalingam, T.S., Cohen, A.N., Chakrabarti, R., Srivatsan, E.S., Wang, M.B., 2005. Curcumin suppresses growth of head and neck squamous cell carcinoma. Clin. Cancer Res. 11(19 Pt 1), 6994–7002. https://doi.org/10.1158/1078-0432.CCR-05-0301

Lund, K.C., Pantuso, T., 2014. Combination Effects of Quercetin, Resveratrol and Curcumin on In Vitro Intestinal Absorption. J. Restor. Med. 3(1), 112-120. https://doi.org/10.14200/jrm.2014.3.0108

Masuda, T., Maekawa, T., Hidaka, K., Bando, H., Takeda, Y., Yamaguchi, H., 2001. Chemical Studies on Antioxidant Mechanism of Curcumin: Analysis of Oxidative Coupling Products from Curcumin and Linoleate. J. Agric. Food Chem. 49(5), 2539-2547. https://doi.org/10.1021/jf001442x

McClements, D., 2012. Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft Matter, 8(6), 1719-1729. https://doi.org/ 10.1039/c2sm06903b

Merisko-Liversidge, E., Liversidge, G.G., Cooper, E.R., 2003. Nanosizing: a formulation approach for poorly-water-soluble compounds. Eur. J. Pharm. Sci. 18(2), 113-120. https://doi.org/10.1016/s0928-0987(02)00251-8

Miller, D.A., DiNunzio, J.C., Yang, W., McGinity, J.W., Williams, R.O.3rd, 2008. Enhanced in vivo absorption of itraconazole via stabilization of

supersaturation following acidic-to-neutral pH transition. Drug Dev. Ind. Pharm. 34, 890–902. https://doi.org/10.1080/03639040801929273

1150 Modasiya, M.K., Patel, V.M., 2012. Studies on solubility of curcumin. Int. J. Pharm. Life Sci. 3(3), 1490-1497. http://www.ijplsjournal.com/issues%20PDF%20files/march%202012/1.pdf

Moghadamtousi, S.Z., Kadir, H.A., Hassandarvish, P., Tajik, H., Abubakar, S., Zandi, K., 2014. A Review on Antibacterial, Antiviral, and Antifungal Activity of Curcumin. BioMed Res. Int. 2014:186864.
1155 https://doi.org/10.1155/2014/186864

Mukundan, M.A., Chacko, M.C., Annapurna, V.V., Krishnaswamy, K., 1993. Effect of turmeric and curcumin on BP-DNA adducts. Carcinogenesis. 14(3), 493-496. https://doi.org/10.1093/carcin/14.3.493

Müller, R.H., Gohla, S., Keck, C.M., 2011. State of the art of nanocrystals –
1160 Special features, production, nanotoxicology aspects and intracellular delivery. Eur. J. Pharm. Biopharm. 78(1), 1-9. https://doi.org/10.1016/j.ejpb.2011.01.007

Murugan, P., Pari, L., 2006. Effect of tetrahydrocurcumin on plasma antioxidants in streptozotocin–nicotinamide experimental diabetes. J. Basic
1165 Clin. Physiol. Pharmacol. 17 (4), 231–44. https://doi.org/10.1515/jbcpp.2006.17.4.231

Mutsuga, M., Chambersm J.K., Uchida, K., Tei, M., Makibuchi, T., Mizorogi, T., Takashima, A., Nakayama, H., 2012. Binding of curcumin to senile plaques and cerebral amyloid angiopathy in the aged brain of various animals and to
1170 neurofibrillary tangles in Alzheimer's brain. J. Vet. Med. Sci. 74, 51-57. https://doi.org/10.1292/jvms.11-0307

Mythri, R.B., Harish, G., Dubey, S.K., Misra, K., Bharath, M.M., 2011. Glutamoyl diester of the dietary polyphenol curcumin offers improved protection against peroxynitrite-mediated nitrosative stress and damage of
1175 brain mitochondria in vitro: implications for Parkinson's disease. Mol. Cell. Biochem, 347, 135-143. https://doi.org/10.1007/s11010-010-0621-4

Nascimento, G.N.L., Montalvão, E.V., Aversi-Ferreira, T.A., 2012. Study of the Pepsin Enzymatic Activity in in-vitro Dissolution Test of Bromazepam Tablets by UV/VIS Spectrophotometry. J. App. Pharm. Sci. 2(10), 11-15.
1180 https://doi.org/10.7324/JAPS.2012.21002

Onoue, S., Takahashi, H., Kawabata, Y., Seto, Y., Hatanaka, J., Timmermann, B., Yamada, S., 2010. Formulation Design and Photochemical Studies on Nanocrystal Solid Dispersion of Curcumin with Improved Oral Bioavailability.

J. Pharm. Sci. 99(4), 1871-1881. https://doi.org/10.1002/jps.21964

1185 Ozeki, K., Kato, M., Sakurai, Y., Ishigai, M., Kudo, T., Ito, K., 2015. Evaluation of the appropriate time range for estimating the apparent permeability coefficient (Papp) in a transcellular transport study. Int. J. Pharm. 495(2), 963-971. https://doi.org/10.1016/j.ijpharm.2015.09.035

Pal, S., Choudhuri, T., Chattopadhyay, S., Bhattacharya, A., Datta, G.K., Das,
1190 T., Sa, G., 2001. Mechanisms of Curcumin-Induced Apoptosis of Ehrlich's Ascites Carcinoma Cells. Biochem. Biophys. Res. Commun. 288(3), 658-665. https://doi.org/10.1006/bbrc.2001.5823

Paolino, D., Vero, A., Cosco, D., Pecora, T.M.G., Cianciolo, S., Fresta, M., Pignatello, R., 2016. Improvement of Oral Bioavailability of Curcumin upon
1195 Microencapsulation with Methacrylic Copolymers. Front. Pharmacol. 7, 485. https://doi.org/10.3389/fphar.2016.00485

Parikh, A., Kathawala, K., Tan, C.C., Garg, S., Zhou, X., 2016. Development of a novel oral delivery system of edaravone for enhancing bioavailability. Int. J. Pharm. 515(1-2), 490–500. https://doi.org/10.1016/j.ijpharm.2016.10.052

1200 Parikh, A., Kathawala, K., Song, Y., Zhou, X-F., Garg, S., 2018a. Curcumin-loaded self-nanomicellizing solid dispersion system: part I: development, optimization, characterization, and oral bioavailability. Drug Deliv. Transl. Res. 8(5), 1389-1405. https://doi.org/10.1007/s13346-018-0543-3

Parikh, A., Kathawala, K., Li, J., Chen, C., Shan, Z., Cao, X., Zhou, X-F., Garg,
1205 S., 2018b. Curcumin-loaded self-nanomicellizing solid dispersion system: part II: in vivo safety and efficacy assessment against behavior deficit in Alzheimer disease. Drug Deliv. Transl. Res. 8(5), 1406-1420. https://doi.org/10.1007/s13346-018-0570-0.

Parsamanesh, N., Moossavi, M., Bahrami, A., Butler, A.E., Sahebkar, A.,
1210 2018. Therapeutic potential of curcumin in diabetic complications. Pharmacol. Res. 136, 181-193. https://doi.org/10.1016/j.phrs.2018.09.012

Patil, S., Choudhary, B., Rathore, A., Roy, K., Mahadik, K., 2015. Enhanced oral bioavailability and anticancer activity of novel curcumin loaded mixed micelles in human lung cancer cells. Phytomedicine, 22(12), 1103-1111.
1215 https://doi.org/10.1016/j.phymed.2015.08.006

Peng, S., Zou, L., Liu, W., Li, Z., Liu, W., Hu, X., Chen, X., Liu, C., 2017. Hybrid liposomes composed of amphiphilic chitosan and phospholipid: Preparation, stability and bioavailability as a carrier for curcumin. Carbohydr. Polym. 156, 322-332. https://doi.org/10.1016/j.carbpol.2016.09.060

1220 Peng, S., Li, Z., Zou, L., Liu, W., Liu, C., McClements, D.J., 2018.

Enhancement of Curcumin Bioavailability by Encapsulation in Sophorolipid-Coated Nanoparticles: An in Vitro and in Vivo Study. J. Agric. Food Chem. 66(6), 1488-1497. https://doi.org/10.1021/acs.jafc.7b05478

Perkins, S., Verschoyle, R., Hill, K., Parveen, I., Threadgill, M.D., Sharma, R.A., Williams, M.L., Steward, W.P., Gescher, A.J., 2002. Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. Cancer Epidemiol. Biomarkers Prev. 11 (6), 535–540. https://cebp.aacrjournals.org/content/11/6/535.long

Petchsomrit, A., Sermkaew, N., Wiwattanapatapee, R., 2015. Hydroxypropylmethyl cellulose-based sponges loaded self-microemulsifying curcumin: Preparation, characterization, and in vivo oral absorption studies. J. App. Polym. Sci. 133(6), 42966. https://doi.org/10.1002/app.42966

Pfeiffer, E., Hoehle, S.I., Walch, S.G., Riess, A., Sólyom, A.M., Metzler, M., 2007. Curcuminoids form reactive glucuronides in vitro. J. Agric. Food Chem. 55 (2), 538–544. https://doi.org/10.1021/jf0623283

Prasad, S., Tyagi, A., 2015. Curcumin and its analogues: a potential natural compound against HIV infection and AIDS. Food & Funct. 6(11), 3412-3419. https://doi.org/10.1039/c5fo00485c

Prasad, S., Tyagi, A., Aggarwal, B., 2014. Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: the Golden Pigment from Golden Spice. Cancer Res. Treat. 46(1), 2-18. https://doi.org/10.4143/crt.2014.46.1.2

Pinnamaneni, S., Rinaldi, F.A., Jayawickrama, D.A., Li, J., Dali, M.V., 2015. Effect of pepsin on maintaining the supersaturation of the HCl salt of a weakly basic drug: a case study. Pharm. Dev. Technol. 21(3), 311-320. https://doi.org/10.3109/10837450.2014.1003653

Ravindranath, V., Chandrasekhara, N., 1980. Absorption and tissue distribution of curcumin in rats. Toxicology, 16(3), 259-265. https://doi.org/10.1016/0300-483x(80)90122-5

Ravindranath, V., Chandrasekhara, N., 1981. Metabolism of curcumi–studies with [3H]curcumin. Toxicology. 22(4), 337–344. https://doi.org/10.1016/0300-483x(81)90027-5

Ray, B., Bisht, S., Maitra, A., Maitra, A., Lahiri, D.K., 2011. Neuroprotective and neurorescue effects of a novel polymeric nanoparticle formulation of curcumin (NanoCurc (TM)) in the neuronal cell culture and animal model: implications for Alzheimer's disease. J. Alzheimers Dis. 23, 61-77. https://doi.org/10.3233/jad-2010-101374

Rai, D., Singh, J,K., Roy, N., Panda, D., 2008. Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity Biochem. J. 410(1), 147–155. https://doi.org/10.1042/BJ20070891

Reddy, R.C., Vatsala, P.G., Keshamouni, V.G., Padmanaban, G., Rangarajan, P.N., 2005. Curcumin for malaria therapy. Biochem. Biophys. Res. Commun. 326(2), 472–474. https://doi.org/10.1016/j.bbrc.2004.11.051

Righeschi, C., Bergonzi, M.C., Isacchi, B., Bazzicalupi, C., Gratteri, P., Bilia, A., 2016.   Enhanced curcumin permeability by SLN formulation: The PAMPA approach. LWT - Food Sci. Technol. 66, 475-483. https://doi.org/10.1016/j.lwt.2015.11.008

Ruby, A.J., Kuttan, G., Babu, K.D., Rajasekharan, K.N., Kuttan, R., 1995. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer Lett. 94(1), 79-83. https://doi.org/10.1016/0304-3835(95)03827-j

Saeidinia, A., Keihanian, F., Butler, A.E., Bagheri, R.K., Atkin, S.L., Sahebkar, A., 2018. Curcumin in heart failure: A choice for complementary therapy? Pharmacol. Res. 131, 112-119. https://doi.org/10.1016/j.phrs.2018.03.009

Sambuy, Y., De Angelis, I., Ranaldi, G., Scarino, M.L., Stammati, A., Zucco, F., 2005. The Caco-2 cell line as a model of the intestinal barrier: influence of cell and culture-related factors on Caco-2 cell functional characteristics. Cell Biol. Toxicol. 21(1), 1-26. https://doi.org/10.1007/s10565-005-0085-6

Sandur, S.K., Pandey, M.K., Sung, B., Ahn, K.S., Murakami, A., Sethi, G., Limtrakul, P., Badmaev, V., Aggarwal, B.B. 2007. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcinogenesis,28(8), 1765-1773. https://doi.org/10.1093/carcin/bgm123

Schiborr, C., Kocher, A., Behnam, D., Jandasek, J., Toelstede, S., Frank, J., 2014. The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. Mol. Nutr. Food Res. 58(3), 516-527. https://doi.org/10.1002/mnfr.201300724

Senft, C., Polacin, M., Priester, M., Seifert, V., Kögel, D., Weissenberger, J., 2010. The nontoxic natural compound Curcumin exerts anti-proliferative, anti-migratory, and anti-invasive properties against malignant gliomas. BMC Cancer. 10, 491. https://doi.org/10.1186/1471-2407-10-491

Seo, S., Han, H., Chun, M., Choi, H., 2012. Preparation and pharmacokinetic evaluation of curcumin solid dispersion using Solutol® HS15 as a carrier. Int.

1295 J. Pharm. 424(1-2), 18-25. https://doi.org/10.1016/j.ijpharm.2011.12.051

Sharma, O., 1976. Antioxidant activity of curcumin and related compounds. Biochem. Pharmacol. 5(15), 1811-1812. https://doi.org/10.1016/0006-2952(76)90421-4

1300 Sharma, R.A., Euden, S.A., Platton, S.L., Cooke, D.N., Shafayat, A., Hewitt, H.R., Marczylo, T.H., Morgan, B., Hemingway, D., Plummer, S.M., Pirmohamed, M., Gescher, A.J., Steward, W.P., 2004. Phase I Clinical Trial of Oral Curcumin: Biomarkers of Systemic Activity and Compliance. Clin. Cancer Res. 10(20), 6847-6854. https://doi.org/10.1158/1078-0432.ccr-04-0744

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., Srinivas, P.S., 1305 1998. Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers. Planta Medica. 64(04), 353-356. https://doi.org/10.1055/s-2006-957450

Shukla, M., Jaiswal, S., Sharma, A., Srivastava, P.K., Arya, A., Dwivedi, A.K., Lal, J., 2016. A combination of complexation and self-nanoemulsifying drug 1310 delivery system for enhancing oral bioavailability and anticancer efficacy of curcumin. Drug Dev. Ind. Pharm. 43(5), 847-861. https://doi.org/10.1080/03639045.2016.1239732

Singh, R., Lillard, J.W.Jr. 2009. Nanoparticle-based targeted drug delivery. Exp. Mol. Pathol. 86(3), 215-223. https://doi.org/10.1016/j.yexmp.2008.12.004

1315 Siviero, A., Gallo, E., Maggini, V., Gori, L., Mugelli, A., Firenzuoli, F., Vannacci, A., 2015. Curcumin, a golden spice with a low bioavailability. J. Herbal Med. 5(2), 57-70. https://doi.org/10.1016/j.hermed.2015.03.001

Song, I., Cha, J., Choi, M., 2016. Characterization, in Vivo and in Vitro Evaluation of Solid Dispersion of Curcumin Containing d-α-Tocopheryl 1320 Polyethylene Glycol 1000 Succinate and Mannitol. Molecules. 21(10), 1386. https://doi.org/10.3390/molecules21101386

Srimal, R.C., Dhawan, B.N., 1973. Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. J. Pharm. Pharmacol. 25(6), 447-452. https://doi.org/10.1111/j.2042-7158.1973.tb09131.x

1325 Sugiyama, Y., Kawakishi, S., Osawa, T., 1996. Involvement of the β-diketone moiety in the antioxidative Mechanism of Tetrahydrocurcumin. Biochem. Pharmacol. 52(4), 519-525. https://doi.org/10.1016/0006-2952(96)00302-4

Suresh, K., Nangia, A., 2018. Curcumin: pharmaceutical solids as a platform to improve solubility and bioavailability. CrystEngComm, 20(24), 3277-3296. 1330 https://doi.org/10.1039/C8CE00469B

Sun, J., Zhao, Y., Hu, J., 2013. Curcumin inhibits imiquimod-induced psoriasis-like inflammation by inhibiting IL-1beta and IL-6 production in mice. PLoS One. 8(6). e67078. https://doi.org/10.1371/journal.pone.0067078

Teixeira, C.C.C., Mendonça, L.M., Bergamaschi, M.M., Queiroz, R.H.C., Souza, G.E.P., Antunes, L.M.G., Freitas, L.A.P., 2015. Microparticles Containing Curcumin Solid Dispersion: Stability, Bioavailability and Anti-Inflammatory Activity. AAPS PharmSciTech. 17(2), 252-261. https://doi.org/10.1208/s12249-015-0337-6

Tønnesen, H.H., Karlsen, J., 1985. Studies on Curcumin and Curcuminoids .VI. Kinetics of Curcumin Degradation in Aqueous- Solution. Z. Lebensm. Unters. Forsch. 180, 402-404. https://doi.org/10.1007/bf01027775

Türker, S., Onur, E., Ozer, Y., 2004. Nasal route and drug delivery systems. Pharm. World Sci. 26(3), 137-142. https://doi.org/10.1023/b:phar.0000026823.82950.ff

van Breemen, R.B., Li, Y., 2005. Caco-2 cell permeability assays to measure drug absorption. Expert Opin. Drug Metab. Toxicol. 1(2), 175-185. https://doi.org/10.1517/17425255.1.2.175

Vasconcelos, T., Sarmento, B., Costa P., 2007. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov. Today. 12(23-24), 1068-1075. https://doi.org/10.1016/j.drudis.2007.09.005

Vecchione, R., Quagliariello,V., Calabria, D., Calcagno, V., De Luca, E., Iaffaioli, R.V., Netti, P.A., 2016. Curcumin bioavailability from oil in water nano-emulsions: In vitro and in vivo study on the dimensional, compositional and interactional dependence. J. Control. Release. 233, 88-100. https://doi.org/10.1016/j.jconrel.2016.05.004

Venkatesan, N., 1983. Curcumin attenuation of acute adriamycin myocardial toxicity in rats. Br. J. Pharmacol. 124(3), 425-427. https://doi.org/10.1038/sj.bjp.0701877

Venkatesan, N., 2000. Pulmonary protective effects of curcumin against paraquat toxicity. Life Sci. 66(2), PL21-28. https://doi.org/10.1016/s0024-3205(99)00576-7

Venkatesan, N., Punithavathi, D., Arumugam, V., 2000. Curcumin prevents adriamycin nephrotoxicity in rats. Br. J. Pharmacol. 129(2), 231-234. https://doi.org/10.1038/sj.bjp.0703067

Volak, L.P., Ghirmai, S., Cashman, J.R., Court, M.H., 2008. Curcuminoids Inhibit Multiple Human Cytochromes P450, UDP-Glucuronosyltransferase, and Sulfotransferase Enzymes, whereas Piperine Is a Relatively Selective

57

CYP3A4 Inhibitor. Drug Metab. Dispos. 36(8), 1594-1605.
https://doi.org/10.1124/dmd.108.020552

1370 Volpe, D.A., Faustino, P.J., Ciavarella, A.B., Asafu-Adjaye, E.B., Ellison, C.D., Yu, L.X., Hussain, A.S., 2007. Classification of Drug Permeability with a Caco-2 Cell Monolayer Assay. Clin. Res. Regulat. Aff. 4(1), 39-47. https://doi.org/10.1080/10601330701273669

1375 Wahlang, B., Pawar, Y., Bansal, A., 2011. Identification of permeability-related hurdles in oral delivery of curcumin using the Caco-2 cell model. Eur. J. Pharm. Biopharm. 77(2), 275-282. https://doi.org/10.1016/j.ejpb.2010.12.006

Wahlström, B., Blennow, G., 1978. A Study on the Fate of Curcumin in the Rat. Acta Pharmacol Toxicol (Copenh). 43(2), 86-92. https://doi.org/10.1111/j.1600-0773.1978.tb02240.x

1380 Wan, K., Sun, L., Hu, X., Yan, Z., Zhang, Y., Zhang, X., Zhang, J., 2016. Novel nanoemulsion based lipid nanosystems for favorable in vitro and in vivo characteristics of curcumin. Int. J. Pharm. 504(1-2), 80-88. https://doi.org/10.1016/j.ijpharm.2016.03.055

Wang, Y.J., Pan, M.H., Cheng, A.L., Lin, L.I., Ho, Y.S., Hsieh, C.Y., Lin, J.K., 1385 1997. Stability of curcumin in buffer solutions and characterization of its degradation products. J. Pharm. Biomed. Anal. 15, 1867-1876. https://doi.org/10.1016/s0731-7085(96)02024-9

Wang, J., Ma, W., Tu, P., 2015. The mechanism of self-assembled mixed micelles in improving curcumin oral absorption: In vitro and in vivo. Colloids Surf. B: Biointerfaces, 133, 108-119.
1390 https://doi.org/10.1016/j.colsurfb.2015.05.056

Wang, Y-H, Ke, X-M, Zhang, C-H, Yang, R-P., 2017a. Absorption mechanism of three curcumin constituents through in situ intestinal perfusion method. Braz. J. Med. Biol. Res. 50(11), E6353. https://doi.org/10.1590/1414-1395 431x20176353

Wang, Y., Wang, C., Zhao, J., Ding, Y., Li, L., 2017b. A cost-effective method to prepare curcumin nanosuspensions with enhanced oral bioavailability. J. Colloid Interface Sci. 485, 91-98. https://doi.org/10.1016/j.jcis.2016.09.003

Wang, R., Han, J., Jiang, A., Huang, R., Fu, T., Wang, L., Zheng, Q., Li, W., Li, 1400 J., 2019. Involvement of metabolism-permeability in enhancing the oral bioavailability of curcumin in excipient-free solid dispersions co-formed with piperine. Int. J. Pharm. 561, 9-18. https://doi.org/10.1016/j.ijpharm.2019.02.027

Williams, J.A., Ring, B.J., Cantrell, V.E., Campanale, K., Jones, D.R., Hall,

1405   S.D., Wrighton, S.A., 2002. Differential modulation of UDP-glucuronosyltransferase 1A1 (UGT1A1)-catalyzed estradiol-3-glucuronidation by the addition of UGT1A1 substrates and other compounds to human liver microsomes. Drug Metab. Dispos. 30(11). 1266–1273. https://doi.org/10.1124/dmd.30.11.1266

1410   Xu, W., Ling, P. and Zhang, T., 2013. Polymeric Micelles, a Promising Drug Delivery System to Enhance Bioavailability of Poorly Water-Soluble Drugs. J. Drug Deliv. 2013, 1-15. https://doi.org/10.1155/2013/340315

Xue, M., Cheng, Y., Xu, L., Zhang, L., 2017. Study of the Intestinal Absorption Characteristics of Curcumin In Vivo and In Vitro. J. App. Pharm. 9(3), 1415   1000246. https://doi.org/10.21065/1920-4159.1000246

Yang, M., Akbar, U., Mohan, C., 2019. Curcumin in Autoimmune and Rheumatic Diseases. Nutrients. 11(5), 1004. https://doi.org/10.3390/nu11051004

Yadav, V.S., Mishra, K.P., Singh, D.P., Mehrotra, S., Singh, V.K., 2005. 1420   Immunomodulatory Effects of Curcumin. Immunopharmacol. Immunotoxicol. 27(3). 485-497 https://doi.org/10.1080/08923970500242244

Zeng, Z., Shen, Z., Zhai, S., Xu, J., Liang, H., Shen, Q., & Li, Q. 2017a. Transport of Curcumin Derivatives in Caco-2 Cell Monolayers. Eur J Pharm Biopharm, 117, 123-131. https://doi.org/10.1016/j.ejpb.2017.04.004

1425   Zeng, X., Cai, D., Zeng, Q., Chen, Z., Zhong, G., Zhuo, J., Gan, H., Huang, X., Zhao, Z., Yao, N., Huang, D., Zhang, C., Sun, D., Chen, Y., 2017b. Selective reduction in the expression of UGTs and SULTs, a novel mechanism by which piperine enhances the bioavailability of curcumin in rat. Biopharm. Drug Dispos. 38(1), 3-19. https://doi.org/10.1002/bdd.2049

1430   Zhang, L., Gu, F.X., Chan, J.M., Wang, A.Z., Langer, R.S., Farokhzad, O.C., 2008. Nanoparticles in Medicine: Therapeutic Applications and Developments. Clin. Pharmacol. Ther. 83(5), 761-769. https://doi.org/10.1038/sj.clpt.6100400

Zhang, Q., Polyakov, N.E., Chistyachenko, Y.S., Khvostov, M.V., Frolova, T.S., Tolstikova, T.G., Dushkin, A.V., Su, W., 2018. Preparation of curcumin self-1435   micelle solid dispersion with enhanced bioavailability and cytotoxic activity by mechanochemistry. Drug Deliv. 25(1), 198-209. https://doi.org/10.1080/10717544.2017.1422298

Figure legends

Figure 1: Keto-Enol tautomerism of curcumin

Figure 2: The structure of Caco-2 cell monolayer grown at a permeable filter support

Figure 3: Sulphation and glucuronidation of curcumin (adapted from Esatbeyoglu et al., 2012)

Figure 4: Reduction and glucuronidation of curcumin (adapted from Esatbeyoglu et al., 2012)

Figure 5: Degradation products of curcumin (adapted from Wang et al., 1997)

Figure 6: Chemical structure of Piperine

Figure 7: Comparison of curcumin oral absorption results of the curcumin + piperine co-administration strategy in rats and humans. (A) 2 g/kg curcumin with 20 mg/kg piperine and (B) 2 g/kg curcumin control administered in rats; (C) 2 g/kg curcumin with 20 mg/kg piperine administered to human volunteers; *: Pure curcumin absorption in humans was reported to be below the detection limit (Shoba et at., 1998).

Figure 8: Comparison of curcumin oral absorption results of different piperine strategies tested in healthy human volunteers. (A) 2 g/kg curcumin with 20 mg/kg piperine and (B) 2 g/kg curcumin control administered in rats (Shoba et at., 1998); (C) 5 mg piperine along with 2 g of curcumin and (D) 2 g curcumin control (Anand et al., 2007).

Figure 9: Comparison of curcumin oral absorption results of two different piperine strategies tested in rats. (A) 2 g/kg curcumin with 20 mg/kg piperine and (B) 2 g/kg curcumin control administered in rats (Shoba et at., 1998); (C) initial dose of 20 mg/kg piperine followed by 200 mg/kg of curcumin after six hours and (D) 200 mg/kg curcumin control (Zeng et al., 2017b).

Figure 10: Graphic scheme of the Curcumin loaded phosphatidylcholine-maltodextrin based lipopolysaccharide nanoparticles (C-LPNCs) formulation (adapted from Chaurasia et al., 2015)

Figure 11: Comparison of curcumin oral absorption results of the novel

1470 curcumin-loaded nanoparticle formulations at the curcumin equivalent oral doses of (A) 50mg/kg for the curcumin loaded lipopolysaccharide nanoparticles, curcumin control concentrations below limit of detection in this study (Chaurasia et al., 2015); (B) 50mg/kg for the nanosuspension prepared by CO_2-assisted in situ nano-amorphization method and (C) curcumin control

1475 (Wang at al., 2017b); (D) 100mg for the Alginate-polysorbate 80 nanoparticles and (E) (Govindaraju et al 2019); and (F) 50mg/kg for the solid lipid nanoparticles (SLNs) with N-carboxymethyl chitosan (NCC) coating, tested in rats, curcumin control concentrations was reported to be below the limit of detection (Baek and Cho,2017).

1480 **Figure 12:** Comparison of curcumin oral absorption of curcumin loaded micelles formulation (A) curcumin oral doses of 10 mg/kg for curcumin-loaded mixed micelle and (B) curcumin control (Patil et al., 2015); (C) 100mg/kg for the curcumin loaded sophoroliplid-coated nanomicelles and (D) curcumin control (Schiborr et al., 2014); (E) 50mg/kg for the self-assembled curcumin-

1485 loaded polymeric micelle, concentration of curcumin from the control sample was reported to be below the limit of detection (Wang et al., 2015).

Figure 13: Comparison of curcumin oral absorption results of the novel nanoemulsion formulations (A) at an oral dose of 8mg/kg for Chitosan coated, piperine loaded oil in water nanoemulsion (B) curcumin control (Vecchione et

1490 al., 2016) and (C) oral dose of 100mg/kg of curcumin-phospholipid complex incorporated self-nanoemulsion, curcumin control values was reported to be below the limit of detection (Shukla et al., 2016).

Figure 14: Comparison of curcumin oral absorption results of the novel microemulsion formulations at the curcumin equivalent doses of (A) 50mg/kg

1495 for the self-emulsifying microemulsion and (B) curcumin control (Dhumal et al.,2015) and (C) 12.5 mg/kg for the HPMC sponge entrapped self-microemulsifying curcumin and (D) curcumin control (Petchsomrit et al., 2015).

Figure 15: Comparison of the curcumin oral absorption results at the

1500 curcumin equivalent oral doses of (A) 8mg/kg for the curcumin-piperine loaded nanoemulsion formulation (Vecchione et al., 2016) and (B) 100mg/kg for the curcumin-piperine loaded solid dispersion formulation (Wang et al., 2019).

Figure 16: Comparative graph of curcumin oral absorption results of the novel

1505 solid dispersion formulations at the curcumin equivalent oral doses of: (A) 47mg/kg for Soluplus containing self-nanomicellizing solid dispersion and (B) curcumin control (Parikh et al., 2018a); (C) 150mg/kg for ball milled curcumin mixed with Na_2GA in a solid dispersion and (D) curcumin control (Zhang et al., 2018) and (E) 100mg/kg for co-amorphous curcumin-piperine solid dispersion,

1510 curcumin levels from the control sample were below the limit of detection; The AUC_{0-t} values of the pure curcumin(control) of this study was reported to be below the limit of detection (Wang et al., 2019).

Figure 17: Comparison of curcumin oral absorption results of the different curcumin oral bioavailability enhancement strategies, at the curcumin oral

1515 doses of: (A) 47mg/kg for the Soluplus containing self-nanomicellising solid dispersion (Parikh et al., 2018a), (B) 50mg/kg for the Nanosuspension prepared by CO_2-assisted in situ nano-amorphization method (Wang et al., 2017b), (C) 8mg/kg for curcumin+piperine loaded nanoemulsion with thiol modified chitosan coating (Vecchione et al., 2018), (D) 100mg/kg for the co-

1520 amorphous curcumin-piperine solid dispersion (Wang et al., 2019) and (E) 50mg/kg for the self-emulsifying microemulsion (Dhumal et al., 2015).
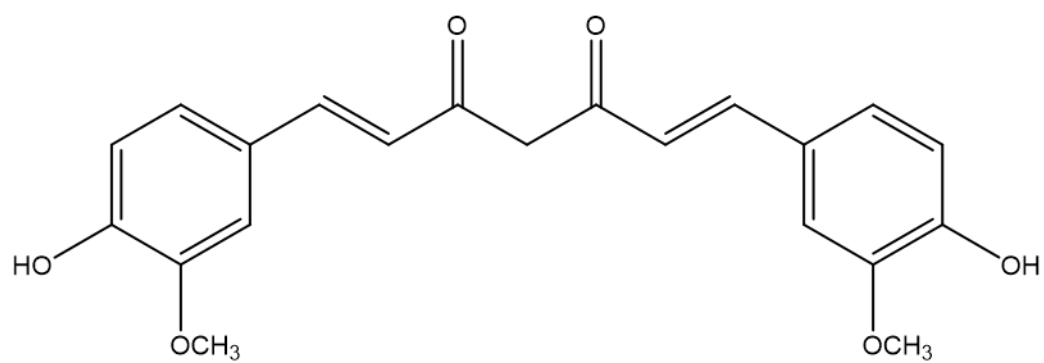
Keto form of Curcumin
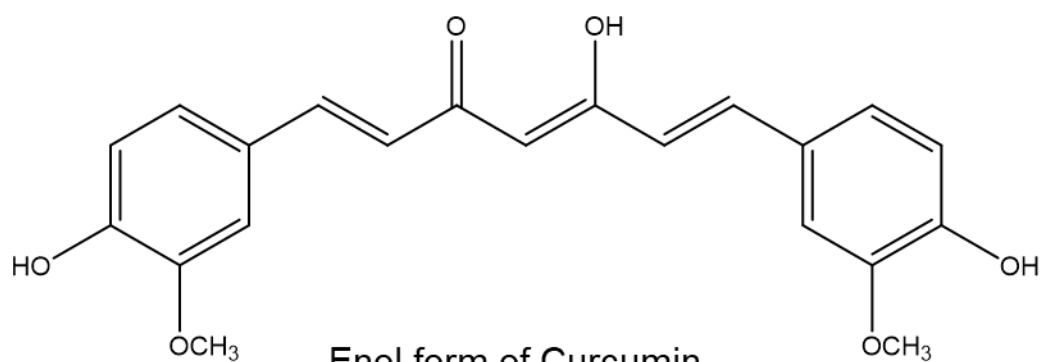
Enol form of Curcumin

1525

Figure 1

1530
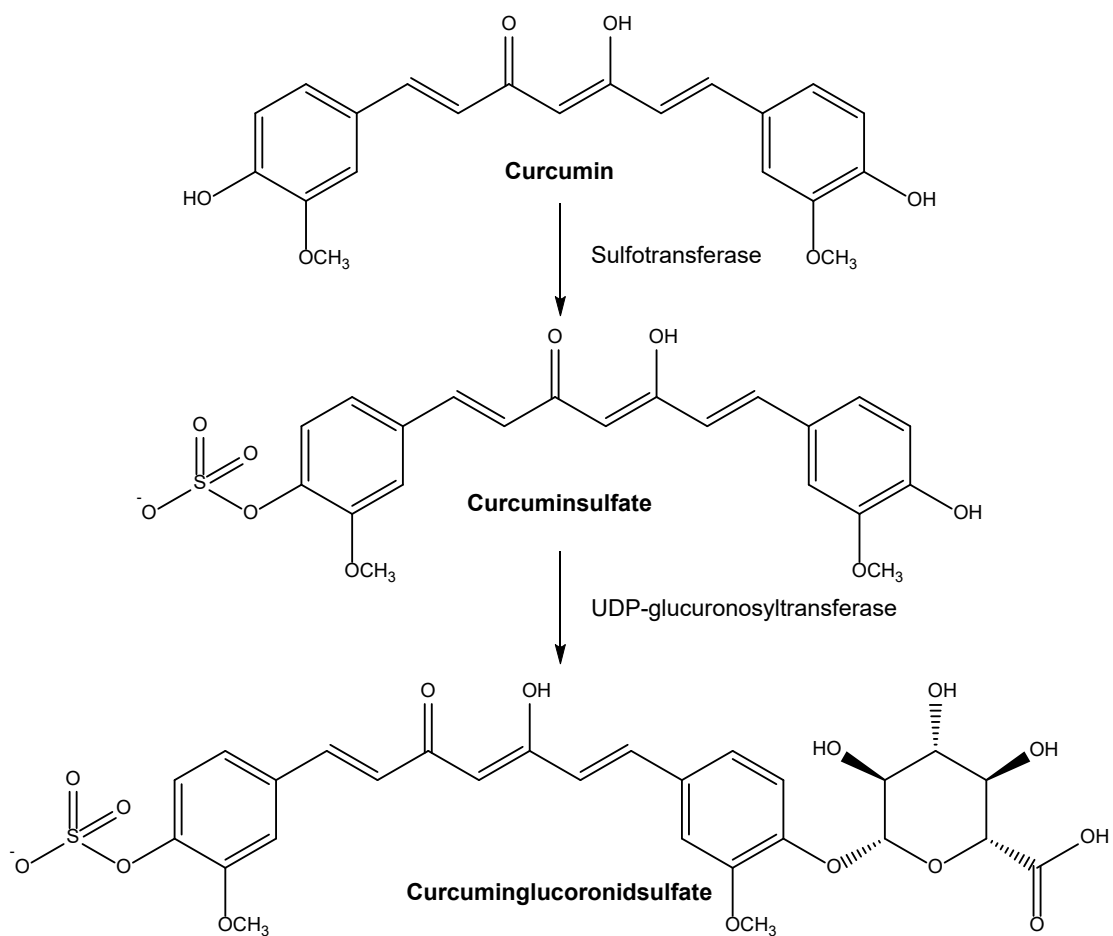
Apical side (A side)

Cell monolayer

Filter

Basolateral side (B side)

Figure 2

1535

Figure 3

1540

Figure 4

Feruloylmethane

Vanillin

Curcumin

Ferulic acid

Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal

1550
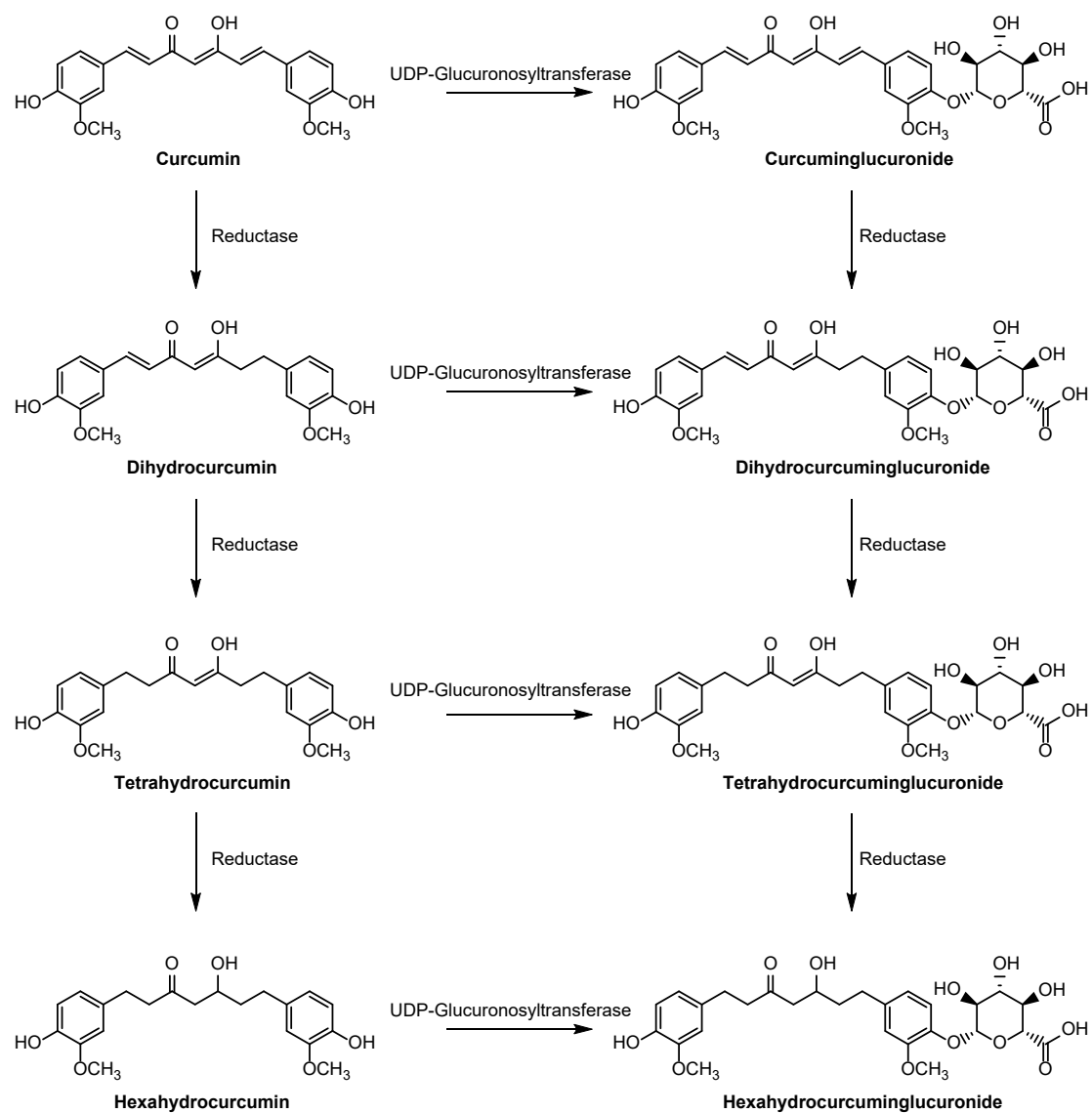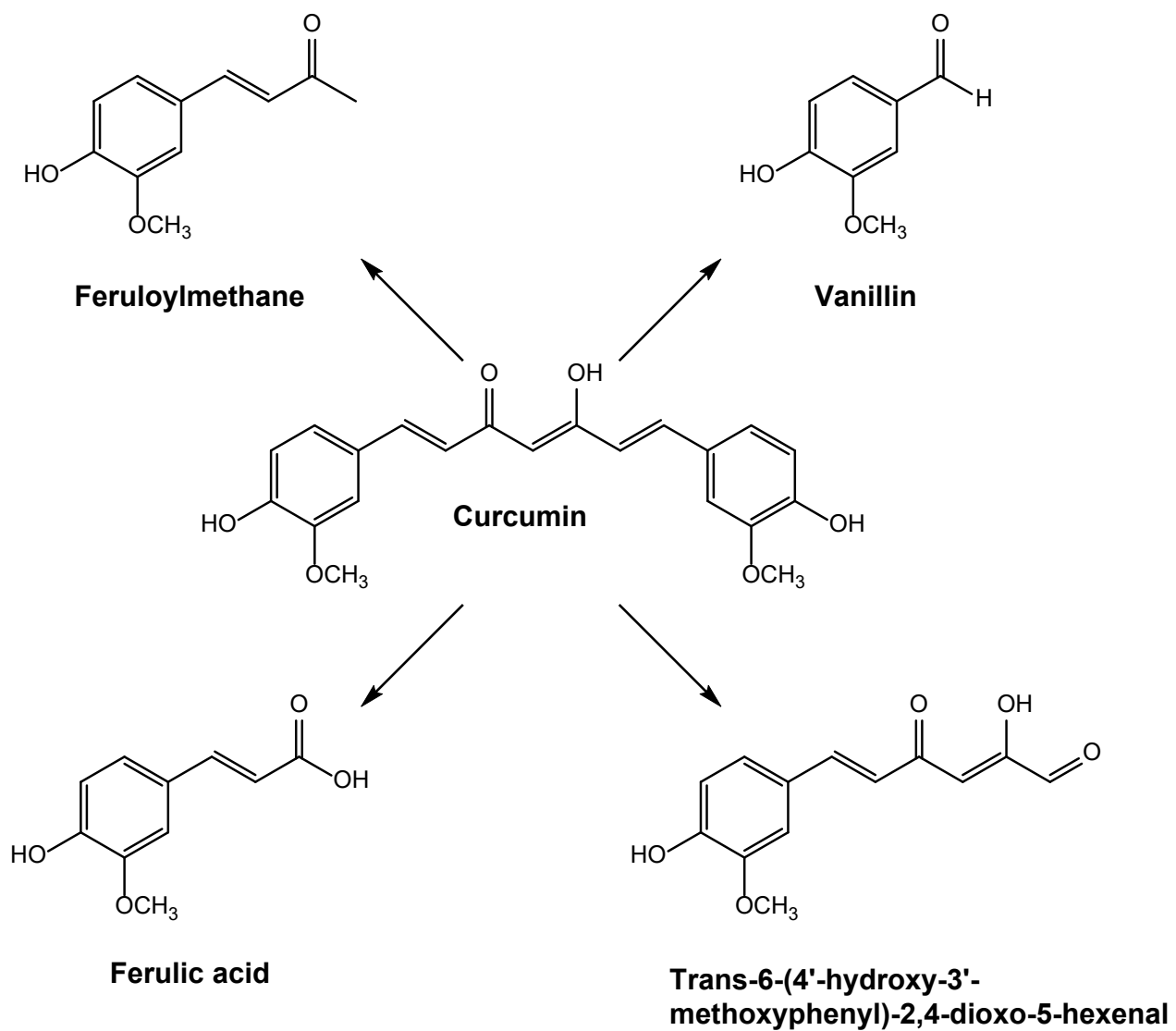
Figure 5

1555
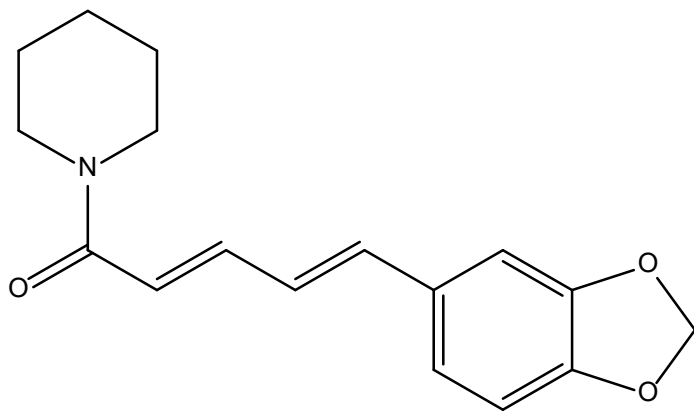
Piperine

1560
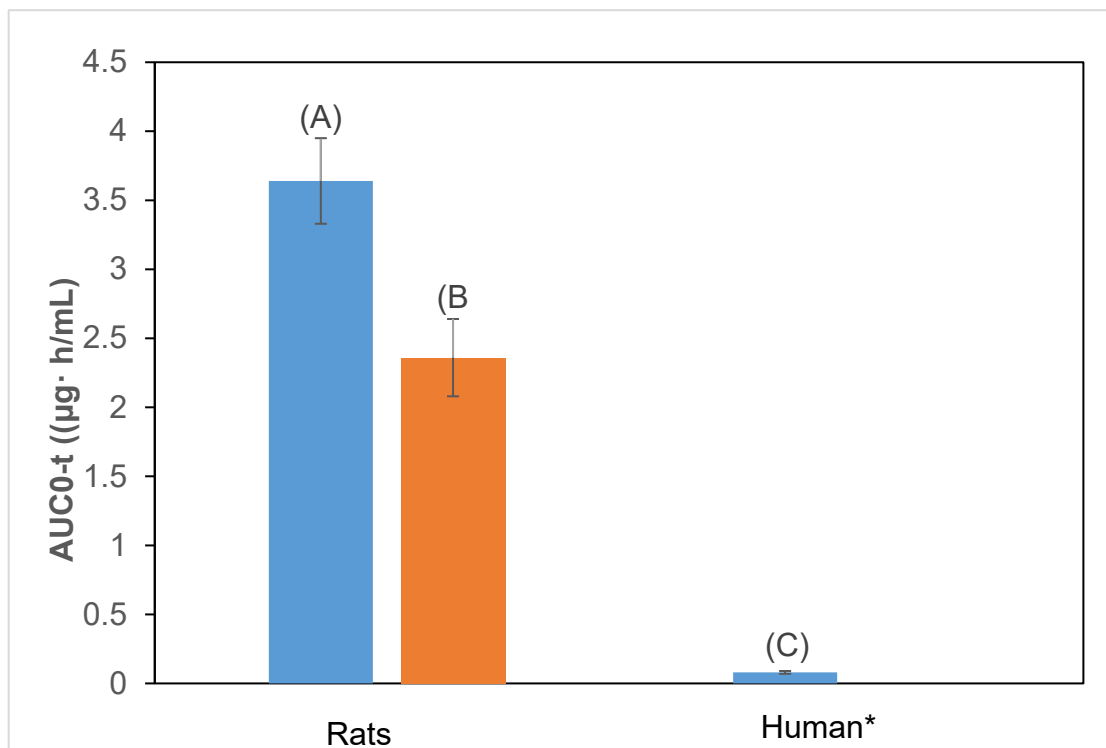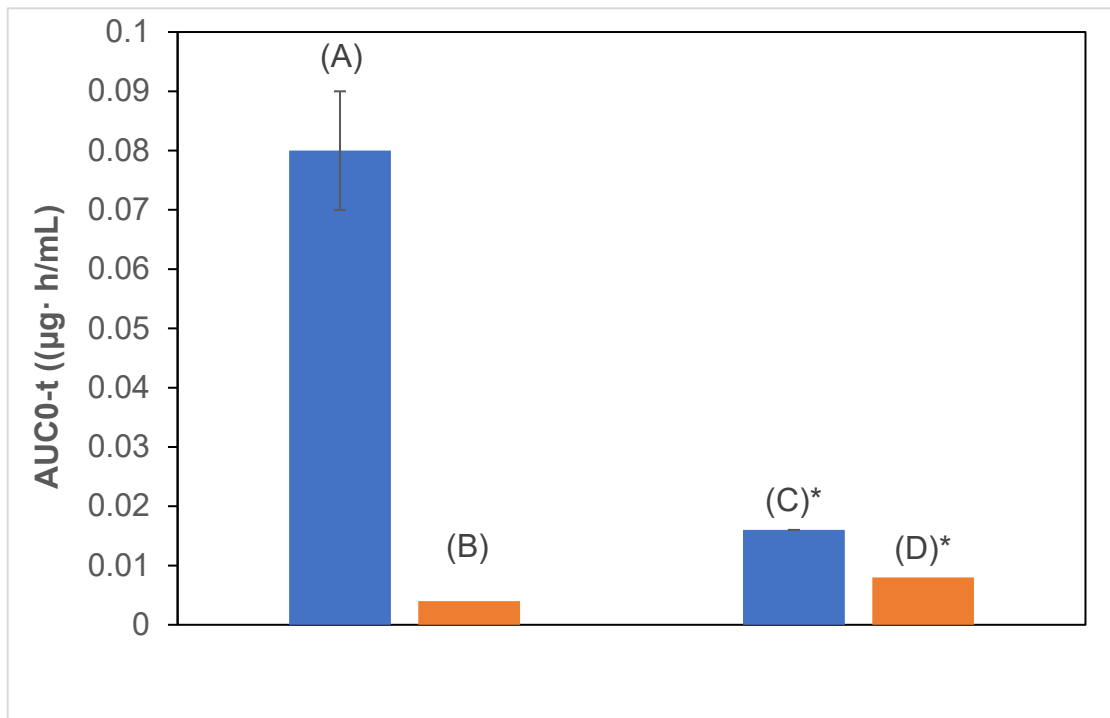
Figure 6

Figure 7

1575 **Figure 8**

* Standard deviation not shown in the publication

Figure 9

Curcumin

Soluthin MD

Poloxamer 188

Oral delivery

↑ curcumin bioavailability

↑ Colon cancer surviving rate
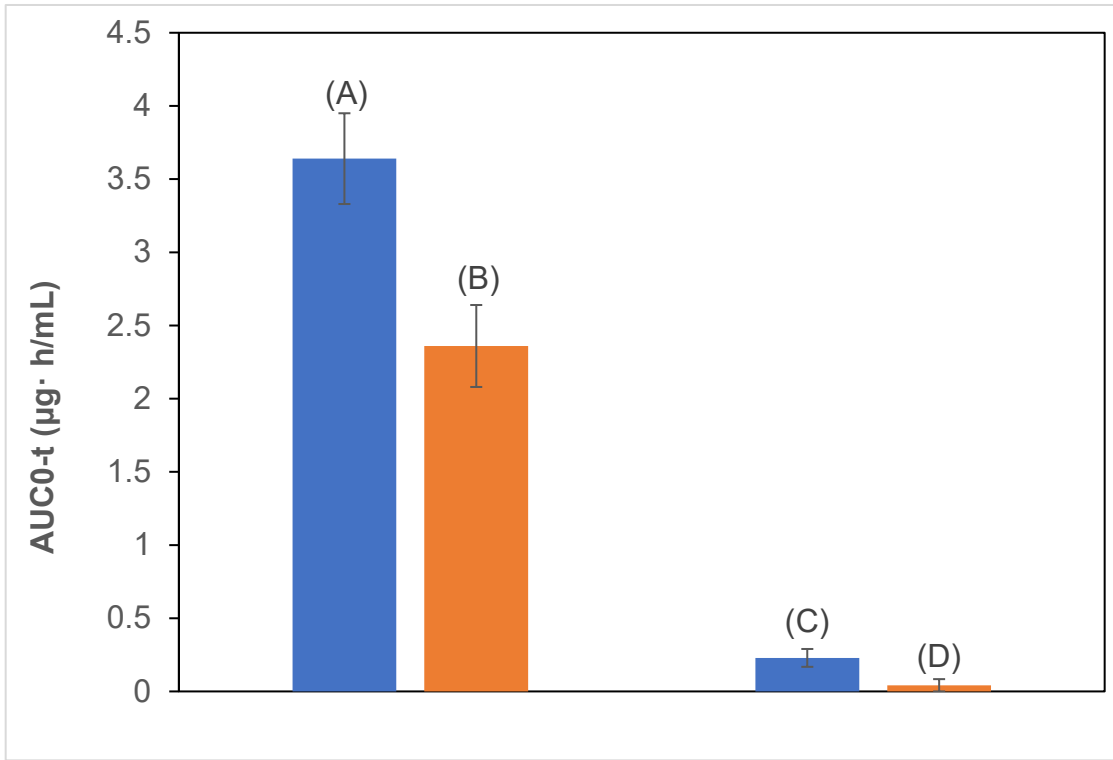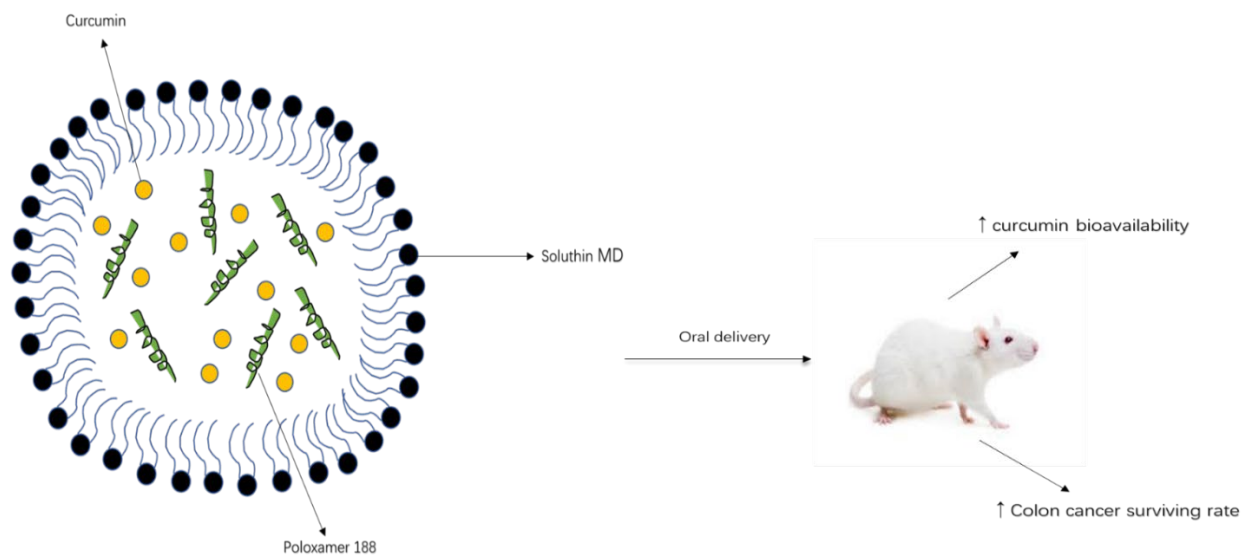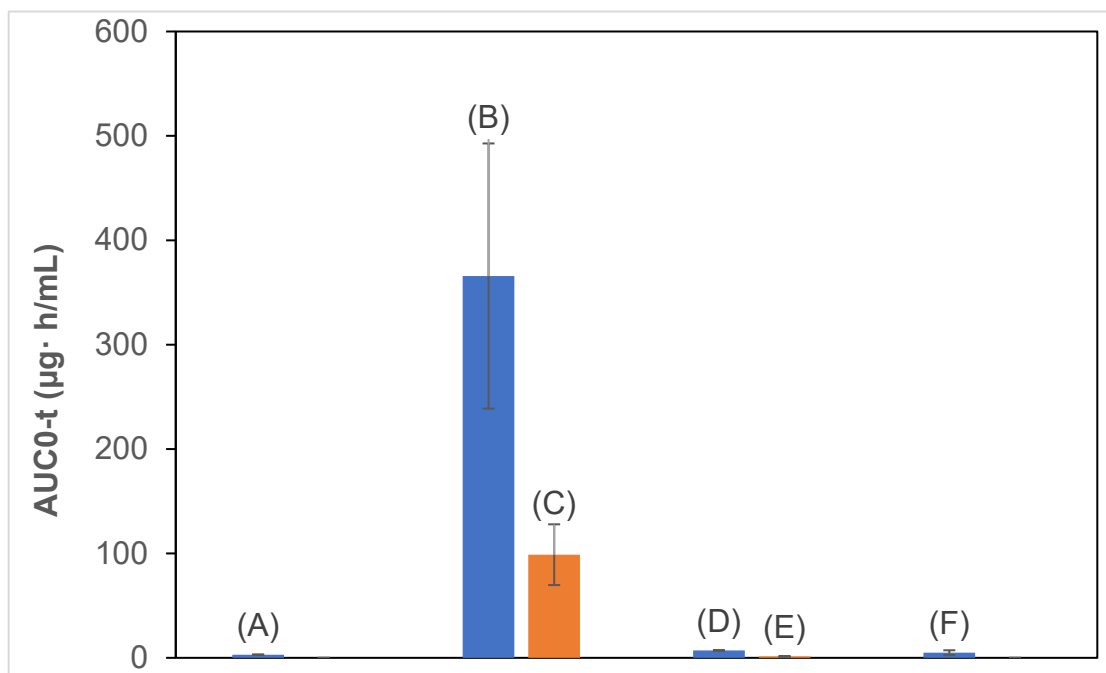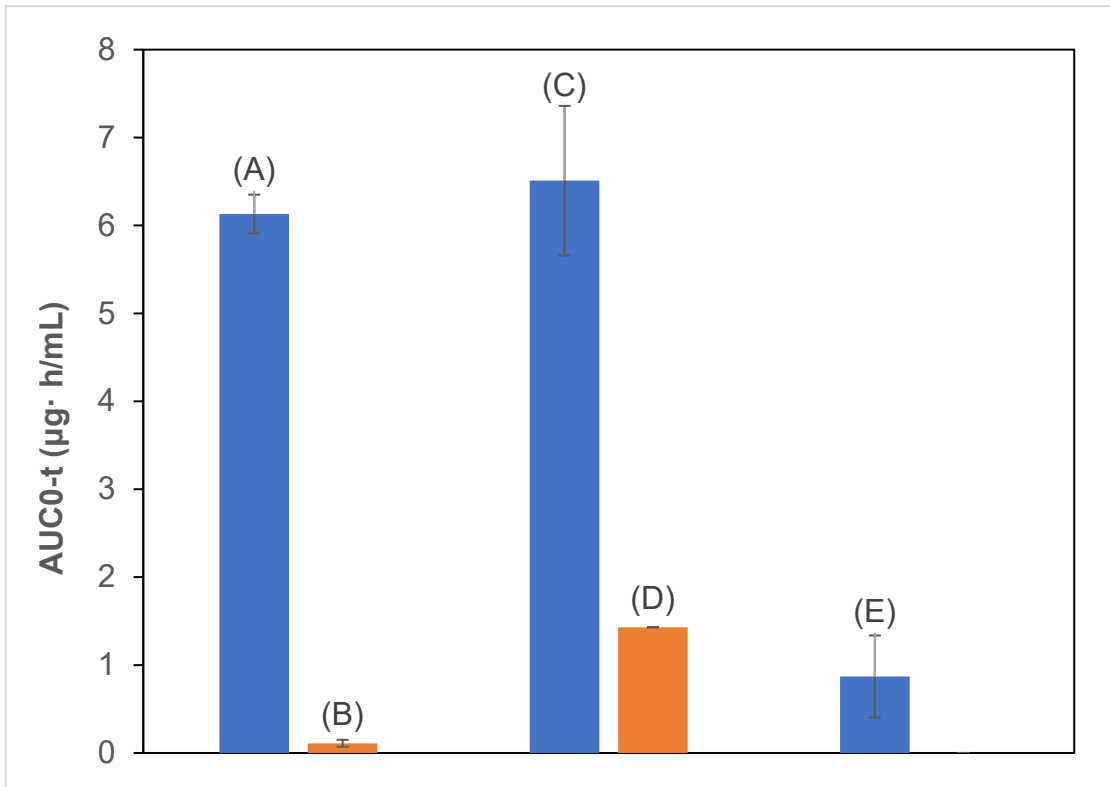
Figure 10

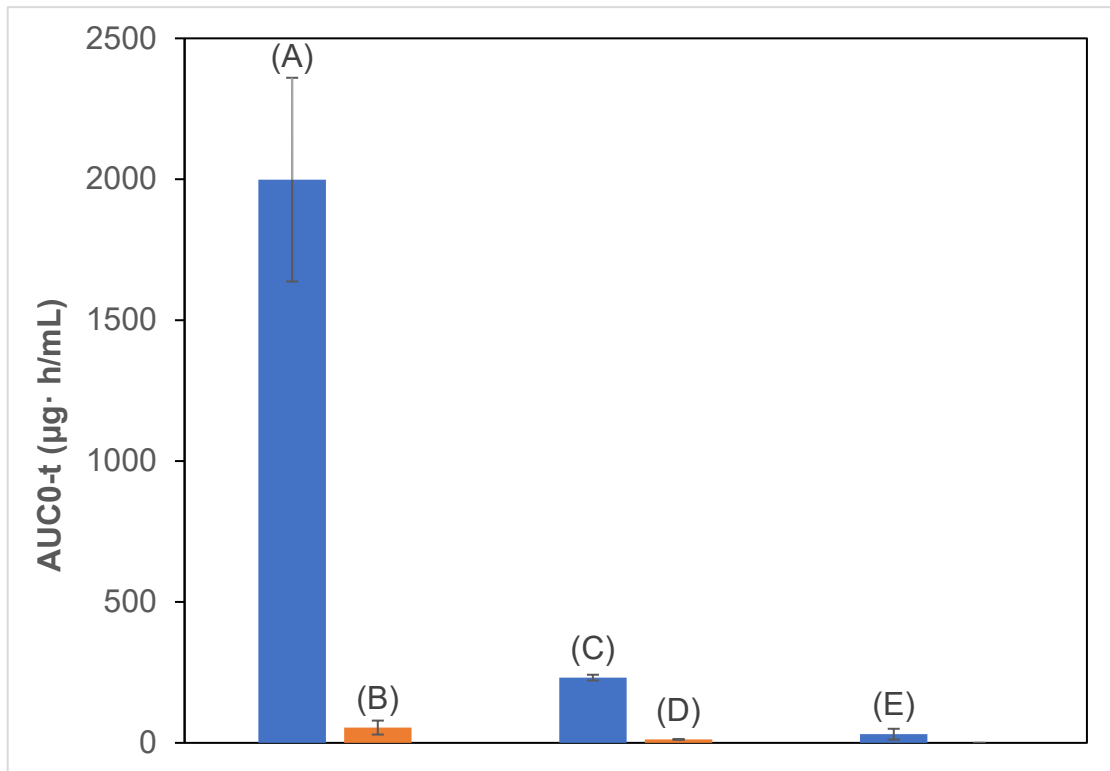**Figure 11**

Figure 12

1600
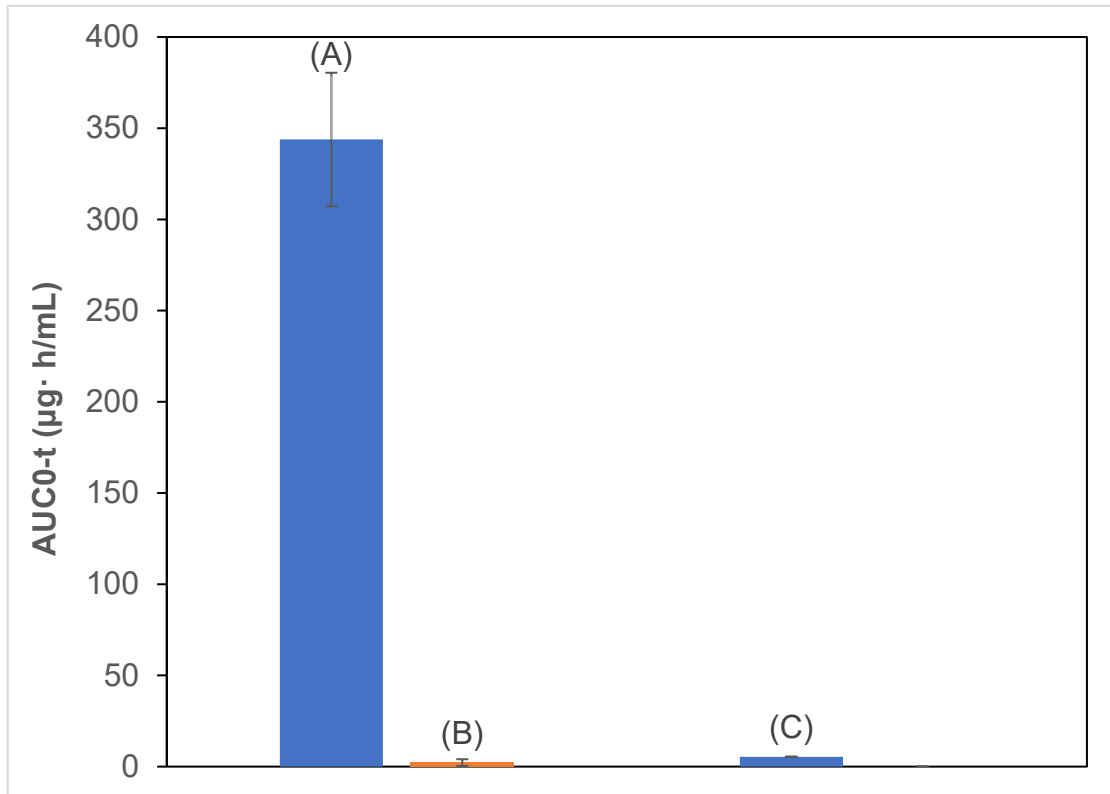
1605

Figure 13

1610
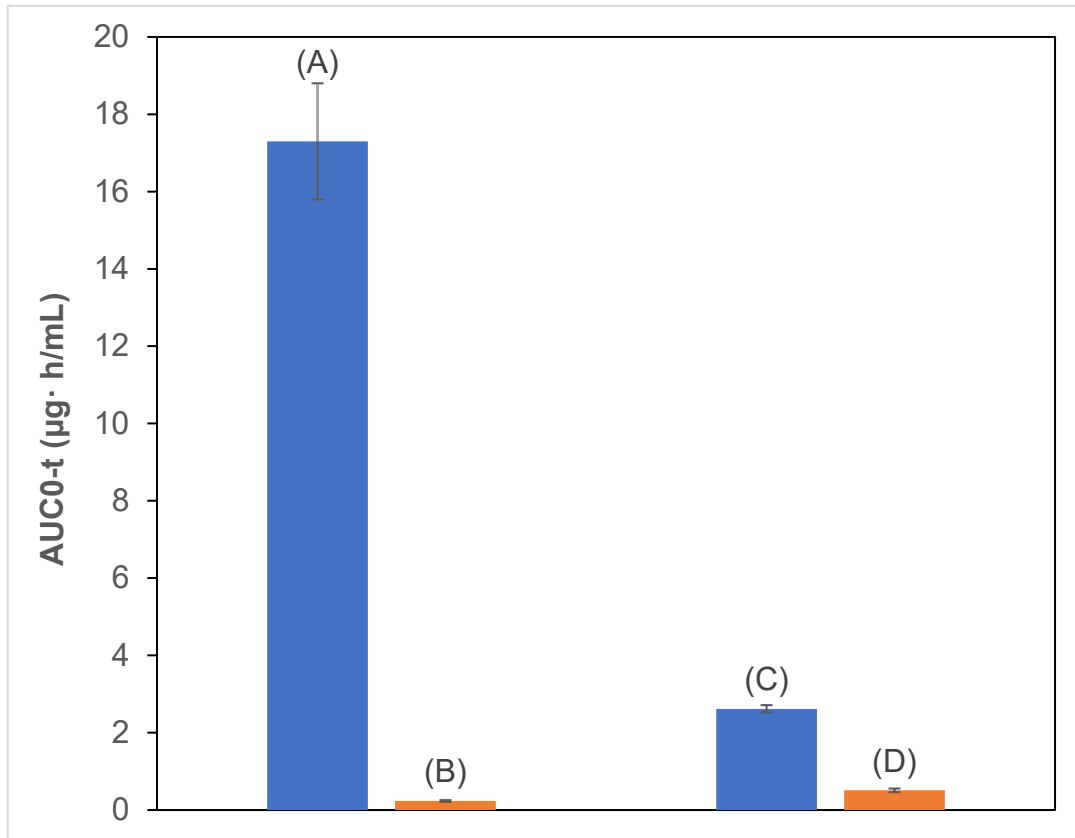
Figure 14
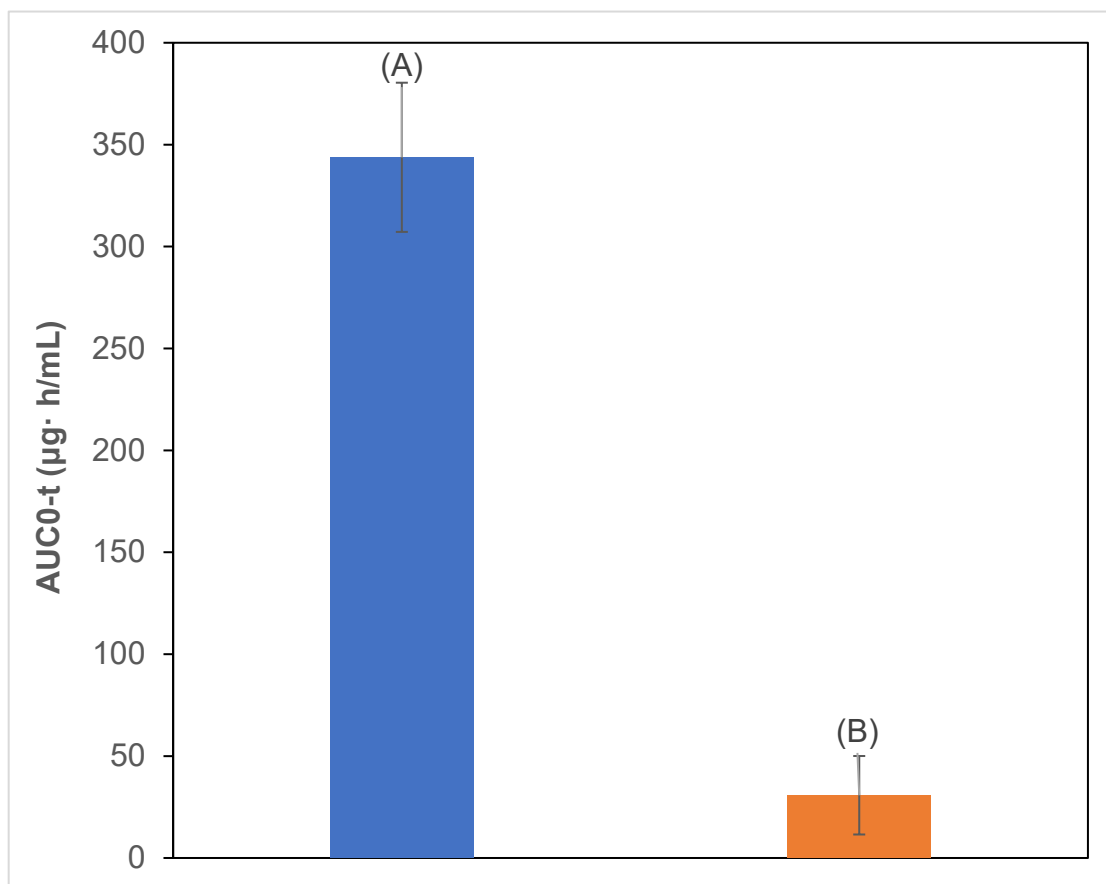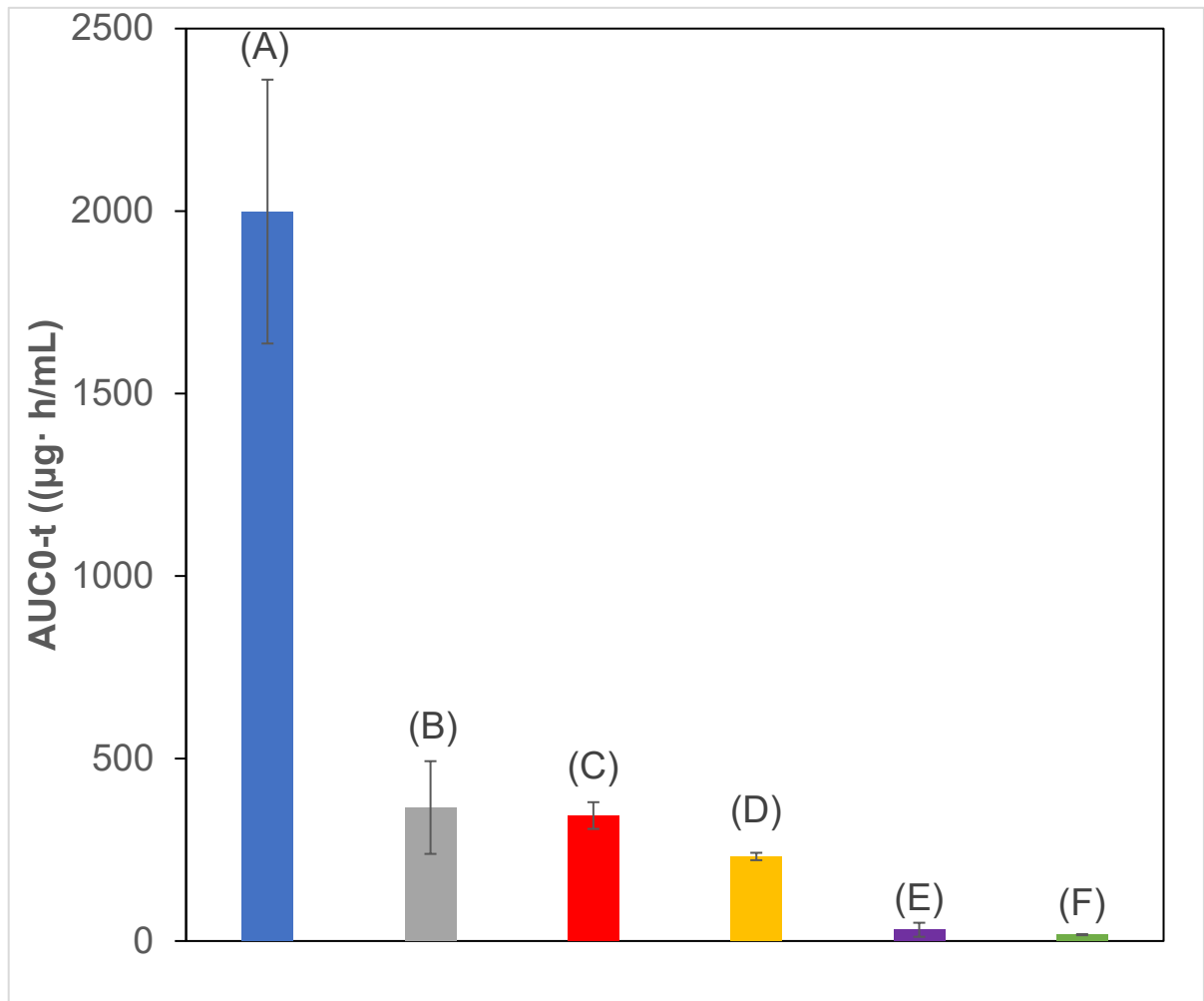
Figure 15

Figure 16

1625

1630   **Figure 17**