ORIGINAL PAPER



Bioaccessibility and bioavailability of polyphenols from sour mangosteen (*Garcinia xanthochymus*) fruit

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Received: 10 January 2020 / Accepted: 13 May 2020 / Published online: 20 May 2020 © Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Sour mangosteen fruits are good dietary sources of polyphenols with various health benefits. To understand the effects of dietary polyphenols on human health it is essential to determine their stability and fate in the lumen. In the present study, we evaluated the bioaccessibility and bioavailability of fruit peel and rind phenolic extract by in vitro gastrointestinal and in vivo mouse (C57BL/6) models. The results of bioaccessibility of peel showed that epicatechin was highly bioaccessible in oral (97.59% \pm 4.87), gastric (82.09% \pm 4.01) as well as intestinal (41.60% \pm 2.88) phase followed by chlorogenic, syringic and gallic acids whereas, in rind, the gallic acid was highly bioaccessible in oral (66.59% \pm 3.93) and gastric (42.89% \pm 3.01) phase followed by catechin and chlorogenic acid, however, in intestinal phase catechin (30.99% \pm 1.98) was highly bioaccessible followed by gallic acid and chlorogenic acid. Gastric pH also favored the recovery of syringic and sinapic acids. Similar results were also observed in bioavailability study in in-vivo animal model with the T_{max} value of both the epicatechin in peel and the catechin in rind was 2 h with a C_{max} value of 62.03 and 1.10 µg/mL of plasma respectively. To conclude, the sour mangosteen fruit peel and rind polyphenols are stable in gastrointestinal tract environment and their bioaccives are more bioavailable.

Keywords Bioaccessibility · Bioavailability · Garcinia xanthochymus · Pharmacokinetics

Introduction

Fruits and vegetables constitute a major part of the diet as they are low in salts, sugars and fats but rich in dietary fiber, minerals, vitamins and other phytochemicals [38]. Polyphenols, carotenoids, xanthones, tannins, lignans, glucosinolates, betalains, steroids are health beneficent phytochemicals that have a number of biological activities, amongst which polyphenols are the most widely distributed compounds in the plant kingdom [14]. In recent years, polyphenols attracted the attention of many researchers for its physiological functionality. Due to the presence of abundant hydroxyl (–OH) groups in their structure

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phenolics have been reported to show antioxidant potential which is imputed by metal ion chelation and free radical scavenging mechanism [27, 33, 41]. This antioxidative action combats oxidative damages in the body which is a chief cause for diseases such as diabetes, cardiovascular diseases, hypertension, gastrointestinal disorders, neurodegenerative diseases, and cancer [13]. Hence, naturally available herbs are being exploited for these health benefits. The different species of the genus Garcinia are among those herbs widely used for its health benefits as they are rich in phytochemicals. Studies have been reported that the polyphenols isolated from various parts of different species of the genus Garcinia viz., G. gambojia and G. indica, belonging to the family Clusiaceae have antioxidant, anti-obesity, anti-diabetic and other biological properties [8, 16, 22]. However, the pharmacological activities of G. xanthochymus, a perennial plant native to China and Western Ghats of India, especially in Mangalore and Coorg of the same family is not well studied [9]. Earlier studies on G. xanthochymus showed that the wood, fresh leaf and whole fruit are rich source of benzophenones [3], flavonoids [4], and xanthones [5, 48], which support the notion that the different parts of the plant is a good source of bioactive compounds. The consumption of bark, wood and leaf has its own limitations. Limited scientific evidences have been shown on these fruit bioactive components, though, fruit as a whole or its extracts are used traditionally and known to cure various ailments such as fever, stomach problems, skin diseases and also sexual disorders [15, 19, 26].

Further, polyphenols are taken orally for the well-being or the treatment of systemic diseases [25]. Absorption of these compounds into the blood stream, in turn reaching to the target tissues decides whether or not these phytochemicals could produce a clinical effect and how fast it can occur. Most of the polyphenols are poorly absorbed when taken orally, greatly affecting the routine clinical application [23]. This may be because, the molecules of flavonoids and other polyphenol are too large to be absorbed by simple diffusion as they are generally multi-ringed [34], they cannot be subjected to active intestinal uptake as well as in case of some vitamins and minerals [23]. They are also being reported as poorly soluble in water [21]. In addition, most of the polyphenols are present as glycosides or as esters of organic acids in plants [39]. The absorption of glycosylated forms are considered to be too long to be absorbed from the gut unless they are broken down by the intestinal microbes [35].

Nevertheless, the reports on absorption and bioavailability of polyphenols from the gastrointestinal tract are limited although their biological effects depend on their absorption and bioavailability. Though there are very fewer studies on the bioavilability of xanthones from *G. mangosteen* [12, 10], the absorption and bioavailability of polyphenols from Garcina genus are not reported. Thus, we aimed to study the stability, absorption and bioavailability of polyphenols of *G. xanthochymus* fruit by both in vitro bioaccessibility and in vivo bioavailability.

Materials and methods

Materials

Fruits of *G. xanthochymus* were obtained from M/S Alvas Pharmacy, Yogaraja Arogyadhama, Mijar-574225, Dakshina Kannada district, Karnataka, India. HPLC grade chemicals were procured from Sigma-Aldrich Chemicals Pvt. Ltd. (St. Louis, USA) whereas all the analytical and laboratory grade chemicals were procured from Rankem Chemicals (Bengaluru, India), Sisco Research Laboratories Pvt. Ltd. (Bengaluru, India) and Himedia Laboratories Pvt. Ltd. (Bengaluru, India). HPLC column (Luna 5 μ m C18 (2)) was procured from Phenomenex, Hyderabad, India.

Processing of fruits

Fresh, matured and ripened fruits were sorted, washed and different parts of the fruits were separated. The aim of the study was to know the health beneficiary property of peel part of the fruit, which is usually discarded or not used during processing of the fruit. But the rind part of the fruit is used by the local population. Thus, the peel as well as rind part was separated from the whole fruit and used for the study. The peel of the fruit was lyophilized (LPe) as the lyophilization process stabilizes all the bioactives without any major changes [42], the rind part was dried under the sun (SDR) to mimic the usage of the fruit in local population [19] and milled in pulveriser (Pilots India, Thrissur, Kerala, India) to obtain fine powder and the samples were stored in air tight container at - 20 °C for further analyses.

Preparation of defatted samples

The processed fruit parts of *G. xanthochymus* fruits were defatted by using hexane. 10 g of fruit samples (LPe and SDR) were extracted with 200 mL of the hexane for 8 h in dark at room temperature. Further the samples were filtered using Whatman filter paper no. 1. The defatted samples were air dried and stored at -20 °C in an air tight container until use.

Extraction of polyphenols

About 1 g of defatted samples of *G. xanthochymus* fruit parts were extracted in 10 mL of 100% methanol in shaking water bath (Julabo, Seelbach, Germany) at 400 rpm for 8 h at 27 °C for the extraction of polyphenols and concentrated by using rotary evaporator (Hei-VAP Core - hand lift model with G3 vertical glassware, Heidolph, Schwabach, Germany) at 45 °C [43–45].

In vitro gastric digestion

The in vitro digestion was performed according to Wootton et al. [46] with slight modifications. Initially the pH of the fruit extracts were set to 6.9 with 1N HCl, pancreatic α -amylase from porcine (\geq 10 units/mg of solid) was added and incubated at 37 °C for 10 min at 55 rpm which completes salivary phase digestion. Further, to mimic gastric phase digestion the pH of the above samples were adjusted to 2.0 with porcine pepsin prepared with 0.1 M HCl and incubated for 1 h at 37 °C in a shaking water bath at 95 rpm. Then, the pH of the samples were increased to 5.3 with 0.9 M NaHCO₃ followed by the addition of bile salts which includes glycodeoxycholate, taurodeoxycholate, taurocholate and pancreatin. Samples were incubated in a shaking water bath at 95 rpm at 37 °C for 2 h after increasing the pH to 7.4 with 1M NaoH to complete the intestinal phase. After the completion of every digestion, 1 mL of digested sample mixture was taken and the polyphenols were extracted by liquid-liquid extraction using ethyl acetate as described by Tagliazucchi et al. [40] and stored at -20 °C. Ethyl acetate was evaporated under vacuum at 45 °C, dissolved in HPLC grade methanol, filtered through 0.22 µ filters and injected to HPLC (Waters India Pvt. Ltd., Bengaluru, India).

In vivo bioavailability study

The animal study was performed with the approval from Institutional Animal Ethics Committee of CSIR-CFTRI, Mysuru (CFT/IAEC/65/2016). Four weeks-old male C57BL/6 mice weighing 20 ± 2 g were obtained and housed at the animal house facility. Mice were housed in groups in polypropylene cages at relative humidity of 40-70% and temperature of 25 ± 2 °C with 12 h light to 12 h dark cycle. Animals were kept on ad libitum AIN-93 M diet [31] and water for 5 days of acclimatization as well as during the experimental period. A day before the experiment, mice were fasted overnight. On experiment day they were orally administered by gavage with lyophilised phenolics from G. xanthochymus fruit parts dissolved in water to evaluate bioavailability. The bioavailability study time points were 0 min, 10 min, 30 min, 60 min, 120 min, 240 min, 360 min, 480 min, and 1440 min. At each time point, three male mice were used. At appropriate time points after intubation, mice were anaesthetized, blood was drawn from retro-orbital plexus, plasma was separated by centrifugation at $2300 \times g$ for 10 min at room temperature and then stored at -80 °C until further analysis. Polyphenols were determined by HPLC after extraction from plasma using sulfatase and β-glucuronidase [1].

Chromatographic conditions for HPLC analysis of phenolic compounds

The phenolic acids in the plasma were quantified by HPLC analysis. The different standards, fruit extracts, and plasma extracts were subjected to HPLC analysis following the protocol of Singh et al. [37] with few modifications. HPLC system [Shimadzu LC-10AVp (Gradient System PDA, RID, UV)] on a reversed-phase C18 column (250×4.6 mm, Phenomenex, USA) was used in the analysis. Gradient program was used with the mobile phase consists of 65% methanol as solvent A (pump A) and 2% acetic acid as solvent B (pump B). The samples were eluted according to the following gradient: a linear step from 0 to 45% of solvent A in 5 min, an isocratic step for 15 min and a final linear increase of solvent A to 55% in 10 min. Degassed milliq water was used in the preparation of all solvents. Injection volume was 10 to 20 μ L, which was varied for standards and samples at the flow rate of 1 mL/min, with 45 min run time and the detection was carried out at 280 nm. Different phenolic acids present in the samples were quantified by comparing with the area of standard peaks.

Pharmacokinetic study

Mean concentrations of polyphenols in the plasma were plotted against time. The pharmacokinetic parameters were determined by non-compartmental methods. Area under the concentration-curve AUC0-inf was assessed from the time of dosing and extrapolated to infinity. Analysis was performed using PK Solver 2.0 software [47].

Statistical analysis

All the analyses were done in triplicates and results are represented as mean \pm standard error (S.E.). Differences between samples were determined by multiple range test using SPSS statistics software, version 17.0. P values at <0.5% were regarded as significant.

Results and discussion

Fruits are edible parts of the plant and also form the rich source of bioactive components. Hence various fruits have been investigated for the presence of several bioactives and their biological activities [20]. Different solvents can be used to extract polyphenols, however, according to the literature, methanol extracts more amounts of polyphenols than other solvents [43–45]. Hence, in the present study 100% methanol is used. Indeed, the results of HPLC study (Fig. 1 LPe extract; Fig. 2 SDR extract) showed that peel as well as rind of the fruit G. xanthochymus is rich in polyphenols $(819.26 \pm 23.65 \text{ and } 927.71 \pm 26.78 \text{ mg}/100 \text{ gm of}$ fruit powder). However, the fact that though fruits are rich in bioactives and its in vitro biological potency, it does not assure the same efficacy in in vivo. This may be because the bioactive components that show biological properties have to sustain the challenges in the in vivo system. The bioactive compounds should be stable enough to face and go through the challenges like alterations due to changes in temperature, pH (at different digestive phases), and gut microbiota. In addition, the size and solubility of the bioactives also play an important role in its bioavailability. Smaller sized and water soluble components are easily absorbable than the larger and water insoluble. Hence, in addition to the chemical composition and biological properties, it is also necessary to understand the bioavailability of the bioactive components.

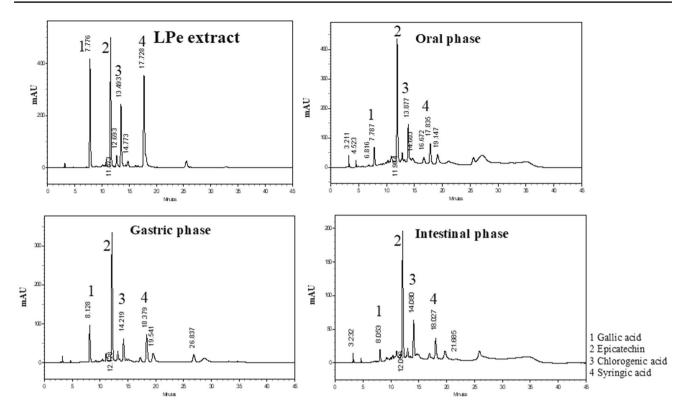


Fig. 1 HPLC chromatograms showing the polyphenol profile before and after in vitro digestion of LPe (Lyophilized peel)

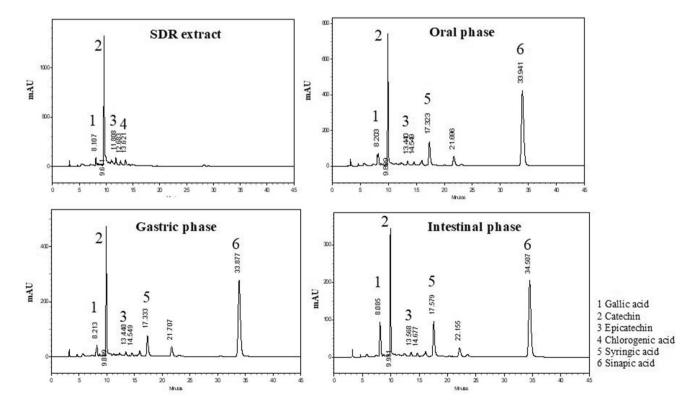


Fig. 2 HPLC chromatograms showing the polyphenol profile before and after in vitro digestion of SDR (Sun dried rind)

Bioaccessibility of polyphenols at different phases of digestion

The use of experimental animals in large number is limited due to ethical issues, thus preliminary studies have adapted in vitro method as an alternative for bioavailability, which is termed as bioaccessibility. Bioaccessibility is an in vitro determination of bioavailability through different digestive phases [11]. The bioaccessibility of a bioactive component was determined in vitro by mimicking the in vivo gastrointestinal tract with physiological condition, i.e., temperature, pH and enzymes in different digestive phases (oral, gastric and intestinal). In the present study, bioaccessibility of potent extracts of different parts of the G. xanthochymus fruit was determined. The HPLC profile of polyphenols from the potent extracts of G. xanthochymus before and after in vitro digestion revealed the presence of 4 and 5 peaks in LPe (Fig. 1) and SDR (Fig. 2) respectively. The percentage of bioaccessibility of different polyphenols detected in both LPe and SDR extracts after in vitro digestion are showed in the Figs. 3 and 4 respectively. The concentrations of epicatechin was found to be high in LPe $(97.59\% \pm 4.87, 82.09\% \pm 4.01)$ and $41.60\% \pm 2.88$ in oral, gastric, and intestinal phase respectively) in all the three digestive phases compared to other polyphenols. In addition, chlorogenic, syringic, and gallic acid were found in decreasing order when compared to the actual concentration in the LPe extract along the 3 phases of digestion. Further, the concentrations of gallic acid was found to be high in oral and gastric phase of SDR $(66.59\% \pm 3.93, \text{ and } 42.89\% \pm 3.01 \text{ respectively})$ where as catechin was found to be high in intestinal phase (30.99% \pm 1.98). Further, the bioaccessibility of SDR showed the presence of chlorogenic acid in addition to the gallic acid, and catechin in all the phases of digestion but in decreasing order when compared to the initial sample without digestion. This decrease in the concentration may be due to the action of digestive enzymes and also pH at different phases of digestion [7]. Furthermore, the acidic pH (2.0) of gastric phase which is less than the pH (3.12 ± 0.12) of initial sample without digestion could recover the syringic acid and synapic acid from SDR which were not detected in the oral phase as well as SDR extract without digestion (Table 1). This was in agreement with the earlier study by Perez-Vicente et al. [30], who reported the similar increase in the concentration of anthocyanins after in vitro gastric digestion. The persistent highest concentration of epicatechin and catechin from LPe and SDR respectively, even after all the phases of digestion suggests the stability and sustainability of these two polyphenols. Since, epicatechin and catechin has sustained the varied enzymes, temperature and pH, it suggests that both have a higher chance of bioavailability in vivo. However, it should be determined in an in vivo system for the validation.

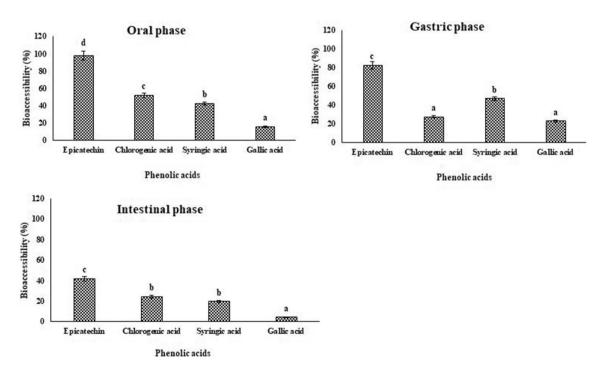


Fig. 3 Bioaccessibility of polyphenols in LPe after simulated in vitro digestion. All the values are mean \pm SEM. Mean values with same superscript letters are not significantly different, whereas those with

different superscript letters are significantly (P < 0.05) different as judged by Duncan's multiple range test

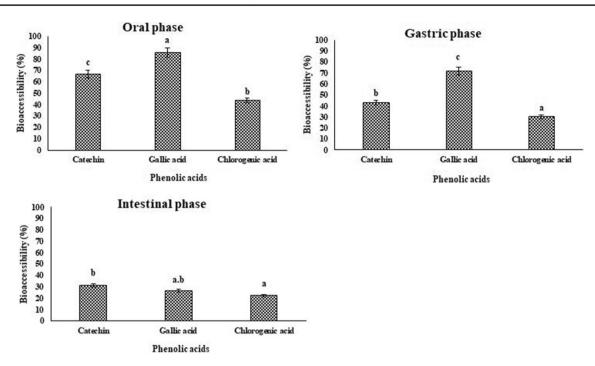


Fig. 4 Bioaccessibility of polyphenols in SDR extract after simulated in vitro digestion. All the values are mean \pm SEM. Mean values with same superscript letters are not significantly different, whereas those

Table 1 Recovery of polyphenols from SDR after in vitro gastric digestion

Phenolic acids	Different phase	of digestion of SDR		
	Oral phase	Gastric phase	Intestinal phase	
Sinapic acid (mg/100 g)	140.55 ± 5.23^{a}	91.07 ± 1.08^{b}	$66.44 \pm 1.25^{\circ}$	
Syringic acid (mg/100 g)	15.73 ± 0.85^{a}	$6.316 \pm 0.06^{\circ}$	10.97 ± 0.95^{b}	

All the values are mean \pm SEM. Mean values with same superscript letters are not significantly different, whereas those with different superscript letters are significantly (P < 0.05) different as judged by Duncan's multiple range test

Bioavailability of polyphenols from LPe and SDR

In continuation with the bioaccessibility, the stability and bioavailability was determined in an in vivo system. The determination of bioavailability is necessary since several other factors such as intestinal microbiota [29] also interfere with the bioavailability of bioactive components. The amount of native compound and its metabolite eliminated from the body can also be determined additionally [32]. It is well established that polyphenols and its metabolites in plasma exists as conjugates of sulfate, glucuronide or mixture of both [28]. Hence, the plasma samples are treated with β -glucuronidase and sulfatase enzymes to release polyphenols from their conjugate forms. This is essential to ensure

with different superscript letters are significantly (P < 0.05) different as judged by Duncan's multiple range test

the estimation of complete polyphenol content present in both free and conjugated forms. Similar to bioaccessibility, six major phenolic compounds were detected in plasma from the mice treated with LPe and SDR respectively. However, cinnamic acid and coumaric acid in LPe and epicatechin as well as coumaric acid in SDR were present in negligible amount. This may be due to biotransformation of phenolics in the mice similar to undetectable levels of vanillin in plasma of rat treated with oat bran phenol rich powder [6] or may be due to inadequate absorption. Further, in untreated rats, the polyphenols were not detected in plasma since the normal diet does not contain noticeable levels of polyphenols.

An increase in the concentration of epicatechin compared to others in the plasma samples of mice treated with LPe extract is comparable with that of in vitro bioaccessibility study (Fig. 5). The epicatechin concentration was observed to be increased at 2 h (62.03 µg/mL), started progressive decrease from 4 h (38.51 µg/mL) and was not detected at 12 h. It also suggests that the T_{max} (the time to maximum concentration in plasma) of epicatechin is at 2 h. The results indicated that epicatechin is more bioavailable followed by gallic acid with C_{max} (the maximum concentration in plasma) 25.13 µg/mL at 1 h T_{max} , chlorogenic acid with C_{max} 12.87 µg/mL at 2 h T_{max} and syringic acid with C_{max} 4.49 µg/ mL at 2 h T_{max} , respectively. It is well known that green tea is rich in epicatechin [17]. Indeed, T_{max} of epicatechin levels in plasma was 1–2 h after administration and was between

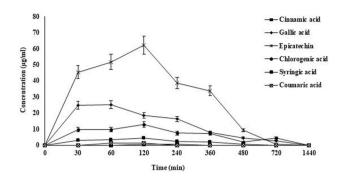


Fig.5 Concentration of different polyphenols at different time intervals after administration of LPe extract. All the values are mean \pm SEM

1.4 and 2.4 h after ingestion of green tea [2]. Furthermore, the elimination of epicatechin in mice were determined by single dose pharmacokinetics parameters like AUC (the area under the concentration-time curve), elimination half-life, elimination rate, volume distribution, and clearance are listed in Table 2. Based on the average plasma phenolic levels, the AUC value of epicatechin ($19.03 \pm 11.2 \mu g/mL/min$) was highest followed by gallic acid ($8.25 \mu g/mL/h$), chlorogenic acid ($5.64 \mu g/mL/h$) and syringic acid ($1.28 \mu g/mL/h$).

In case of mice treated with SDR, the concentration of catechin was found to be increased compared to others in plasma and are comparable with that of bioaccessibility (Fig. 6). The catechin concentration was observed to be increased at 2 h with C_{max} 86.21 µg/mL, started progressive decrease from 4 h (75.51 µg/mL) and was not detected at 12 h. It also suggests that the T_{max} of catechin is at 2 h. The result indicates that catechin is more bioavailable in mice treated with SDR followed by chlorogenic acid with C_{max} 40.30 µg/mL at 2 h T_{max} , gallic acid with C_{max} 14.28 µg/mL at 4 h T_{max} , epicatechin with C_{max} 1.15 µg/mL at 2 h T_{max}

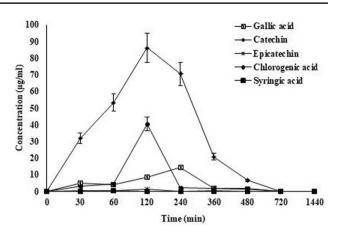


Fig. 6 Concentration of different polyphenols at different time intervals after administration of SDR Note: All the values are mean \pm SEM

and coumaric acid with Cmax 1.10 µg/mL at 2 h Tmax respectively. Studies have reported that catechins are rich in black berry, red wine, dark chocolates, cherry, guava, pear, etc. [18, 25]. Furthermore, the elimination of catechin in mice were determined by single dose pharmacokinetic parameters are listed in Table 3. Based on the average plasma phenolic levels, the AUC value of catechin (21.72 µg/mL/min) was highest followed by chlorogenic acid (3.66 µg/mL/h), gallic acid (2.95 µg/mL/h), and syringic acid (0.07 µg/mL/h). Though, the catechin plays very important role against cancer, obesity, diabetes, hypercholesterolemia.etc., the rich sources of catechin are highly expensive and not affordable in low income group countries. As this fruit is rich in catechins and cost effective, it can be used as an alternate source in these countries. The rind part of the fruit which is dried under the sun and used by the local population showed the presence of catechin. The rind also includes peel part of

Table 2 Single dose pharmacokinetic study of polyphenols in plasma from LPe

Parameters	Phenolic acids						
	Cinnamic acid	Gallic acid	Epicatechin	Chlorogenic acid	Syringic acid	Coumaric acid	
C _{max} (µg/mL)	0.54	25.13	62.02	12.86	4.48	1.3	
T _{max} (min)	720	60	120	120	120	120	
AUC last (µg/mL*min)	0.11	7.5	18.97	4.39	1.14	0.08	
AUC extra (µg/mL*min)	0	0.74	0.05	1.25	0.12	0	
AUC tot (µg/mL*min)	0	8.25	19.03	5.64	1.27	0	
%AUC extra (%)	0	9.01	0.29	22.17	9.83	0	
Lz (µg/h)	0	0	0.01	0	0	0	
t ½ (min)	0	203.65	62.27	320.97	127.71	0	
MRT 0-inf_obs (min)	0	307.42	216.9	478.93	240.79	0	

 C_{max} —the maximum concentration in plasma, T_{max} —the time to C_{max} , AUC last—area under the curve from time 0 to the last measurable concentration, AUC extra—AUC from zero to infinity, AUC tot—total AUC, %AUC extra—percentage of AUC from zero to infinity, Lz—the elimination rate constant, t ½—the elimination half-life, MRT 0-inf_obs—observed mean residence time from zero to infinity

Parameters	Phenolic acids							
	Gallic acid	Catechin	Epicatechin	Chlorogenic acid	Syringic acid	Coumaric acid		
C _{max} (µg/mL)	14.28	86.21	1.15	40.30	0.35	1.10		
T _{max} (min)	240	120	120	120	60	120		
AUC last (µg/mL*min)	2.85	21.17	0.15	3.53	0.04	0.03		
AUC extra (µg/mL*min)	0.10	0.55	0	0.12	0.02	0		
AUC tot (µg/mL*min)	2.95	21.72	0	3.66	0.07	0		
%AUC extra (%)	3.38	2.55	0	3.5	37.09	0		
Lz (µg/h)	0	0.01	0	0	0	0		
t ½ (min)	70.39	67.90	0	88.42	305.25	0		
MRT 0-inf_obs (min)	219.50	197.40	0	175.52	476.14	0		

 Table 3
 Single dose pharmacokinetic study of polyphenols in plasma from SDR

 C_{max} —the maximum concentration in plasma, T_{max} —the time to C_{max} , AUC last—area under the curve from time 0 to the last measurable concentration, AUC extra—AUC from zero to infinity, AUC tot—total AUC, %AUC extra—percentage of AUC from zero to infinity, Lz—the elimination rate constant, t ½—the elimination half-life, MRT 0-inf_obs—observed mean residence time from zero to infinity

the fruit. The peel part which was lyophilyzed in our study showed the presence of epicatechin. Our results were in support with Kofink et al. [24] and Seto et al. [36] where they have reported the epimerization reaction of epicatechin i.e., the conversion of (–)-epicatechin into (–)-catechin under the influence of high temperature. The LPe sample also showed the presence of bioavailable cinnamic acid (C_{max} – 0.54 µg/mL of plasma) which was absent in SDR. These results shows that the fresh fruit of *G. xanthochymus* can have better biologica activity when compared to the processed fruit parts.

Conclusions

Polyphenols are one of the good source of antioxidants and known to have many biological activities. *G. xanthochymus* possess a higher amount of polyphenols. However, their biological activity depends on the amount of bioavailable polyphenols in the in vivo system. Indeed, in the present study both in vitro bioaccessibility and in vivo bioavailability results showed that epicatechin and catechin are highly stable and greatly bioavailable from LPe and SDR parts of the *G. xanthochymus* fruit respectively. Hence, *G. xanthochymus* fruit can be used as an alternate source for epicatechin and catechin instead of green tea and black berry. This is the first report on *G. xanthochymus* fruit polyphenols bioaccessibility and bioavailability which may serve as a platform for further studies on health benefits.

Acknowledgements The authors thank the Head, Department of Biochemistry and Director, CSIR-CFTRI, for providing the infrastructure and facilities to carry out this work. The first author Ms. Janhavi P, thanks DST for financial support in the form of INSPIRE Fellowship. Funding This work was financially supported by the DST under DST INSPIRE Fellowship scheme (No. DST/INSPIRE Fellowship/2014/IF150409).

Compliance with ethical standards

Conflict of interest We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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