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Antioxidant properties of *Prangos ferulacea* (L.) Lind., *Chaerophyllum macropodum* Boiss. and *Heracleum persicum* Desf. from *Apiaceae* family used as food in Eastern Anatolia and their inhibitory effects on glutathione-S-transferase

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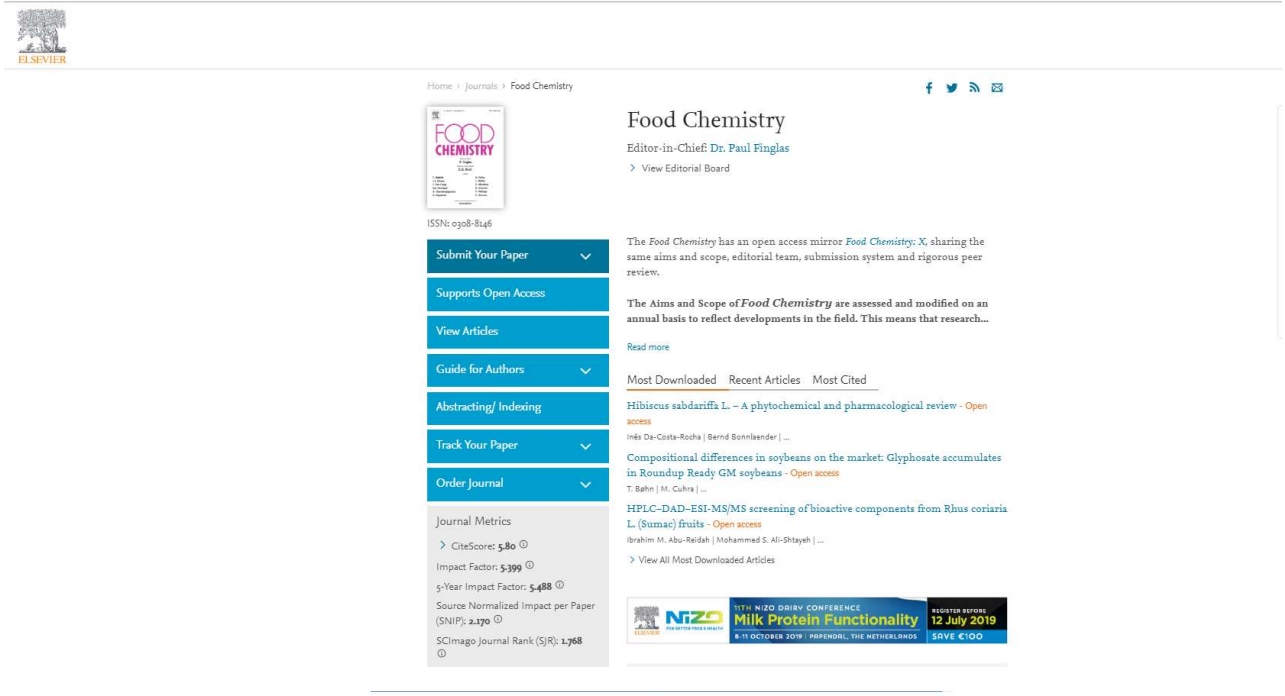
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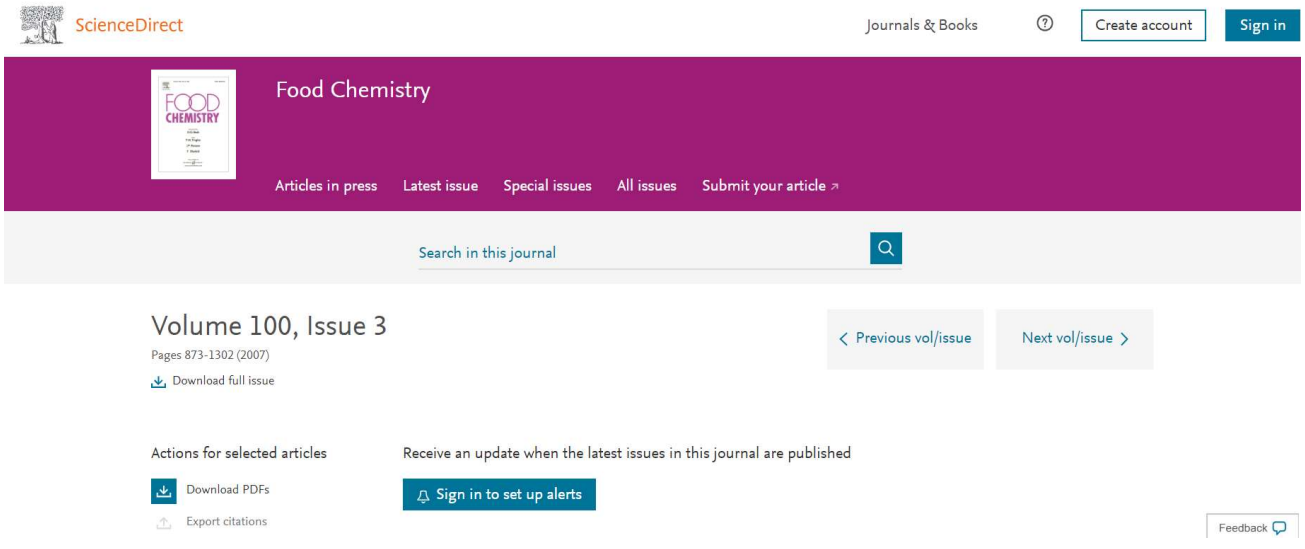
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Abstract

Therapeutic effects of several medicinal plants and vegetables, which are commonly used as food and in folk medicine against many disease, are well known. Antioxidant capacities of *Heracleum persicum* Desf., *Prangos ferulacea* (L.) Lindl., *Chaerophyllum macropodum* Boiss. species from Apiaceae family were evaluated by determining their effects on DPPH radical scavenging, and lipid peroxidation inhibition, as well as their total phenolic contents. Potential natural glutathione-*S*-transferase inhibitors have gained great importance in the last decade especially because of the role of glutathione-*S*-transferases in developing resistance to chemotherapy. Selected plants were therefore further investigated for their influence on the activity of glutathione-S-transferase enzyme.

In comparing antioxidant capacities, *P. ferulacea* was found to be a better antioxidant than the other two plants in the family, with 50% inhibitory concentration values as 0.242 and 0.152 mg/ml for DPPH radical scavenging and lipid peroxidation inhibition, respectively. The same plants were also evaluated for their effects on GST activities and among the studied plants, *P. ferulacea* was the most efficient inhibitor with IC_{50} value of 79.25 μg/ml for GST. *C. macropodum* and *H. persicum* were less effective antioxidants than *P. ferulacea* with IC_{50} values of 0.623 and 0.438 mg/ml for DPPH radical scavenging, respectively, however, they could also be considered as potential GST inhibitors.
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Keywords: Antioxidant; DPPH; Phenolic content; Lipid peroxidation; Glutathione-*S*-transferase; GST; Apiaceae

1. Introduction

Free radicals play a major role in the pathogenesis of many diseases including atherosclerosis, ischemic heart disease, cancer, Alzheimer's, Parkinson's, and even in the aging process (Aruoma, 2003). In cellular defence system, scavenging of free radicals is an important issue affiliated by utilization of both exogenous and endogenous antioxidants. In the last decade, the antioxidants from food resources have attracted a great deal of attention related to their ROS scavenging capacity. In diets, non-enzymatic natural antioxidants such as α-tocopherol (Vitamin E), Vitamin C and quercetin can be consumed as food supplements. Therapeutic effects of several medicinal plants and vegetables, which are commonly used in folk medicine against many diseases, are usually attributed to their phenolic contents and their antioxidant ingredients. Polyphenolic compounds, are defined as substances possessing an aromatic ring with one or more hydroxy substituents and

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are reported to quench oxygen-derived free radicals by donating a hydrogen atom or an electron to the free radical (Halliwell & Gutteridge, 1989; Shahidi & Naczk, 1995).

In this study, three medicinal plants from Apiaceae (Umbellifera) family were collected from Eastern Anatolia, Van region and their antioxidant capacities were investigated. *Prangos ferulacea*, *Chaerophyllum macropodum* and *Heracleum persicum* species were selected because of their common use as food and medicinal remedies in that region. Sayyah, Moaied, and Kamalinejad (2005) have recently reported that acetone extracts of *Heracleum persicum* seeds were effective anticonvulsants. The genus *Prangos* consists of about 30 species, and some of them have been used in folk medicine as emulient, carminative, tonic, antiflatulent, antihelminthic, and antifungal agents (Ceylan, 1987). *C. macropodum* is a common plant used as herbs in cheese preparations, before the flowering period in the Eastern Anatolia. This is the first and only study about the antioxidant capacity of *C. macropodum* and its total phenolics content.

The effects of medicinal plants on glutathione-*S*-transferase (GST) activities were investigated along with their antioxidant capacities, since the GST enzymes account for the defence against oxidative stress, and they detoxify endogenous harmful compounds such as the breakdown products of lipid peroxidation or DNA hydroperoxides (Hayes & Pulford, 1995; Nordberg & Arn'er, 2001). Another reason, to attract the interest on GST activity is the ability of resistant tumor cells to promote GST catalyzed GSH conjugation of the pharmacologically active compounds such as antitumor drugs (Guadiano et al., 2000; Zanden et al., 2004). Therefore, elevated GST activity is regarded as an indicator for the resistance to chemotherapy. In this respect, inhibitory effects of novel antioxidants on GST activity are continuously investigated by researchers (Gyamfi, Ohtani, Shinno, & Aniya, 2004). In this study, the inhibition of sheep liver cytosolic GST activity was investigated in vitro, in order to evaluate potential GST inhibitors which could be used as adjuvant to overcome chemotherapy resistance.

2. Materials and methods

2.1. Materials

Preparative chromatography grade methanol used in the preparation of extracts was purchased from Merck (Darmstadt, Germany). Potassium chloride (KCl), ethylenediaminetetraacetic acid (EDTA), glycerol, bovine serum albumin (BSA), copper sulphate ($CuSO_4$), sodium potassium tartarate, sodium hydroxide (NaOH), sodium carbonate, Tris–HCl, iron sulphate ($FeSO_4 \cdot 7H_2O$), thiobarbituric acid (TBA), ortho-phosphoric acid (H_3PO_4), α-tocopherol, quercetin, 2,2-diphenyl-1-picrylhydrazyl (DPPH), gallic acid, 1-chloro-2,4-dinitrobenzene (CDNB), reduced glutathione (GSH), were purchased from Sigma Chemical Company, (St. Louis, MO, USA). Dimethyl sulphoxide (DMSO) and Folin–Ciocalteau's phenol reagent were purchased from Merck (Darmstadt, Germany). All other chemicals were analytical grade and were obtained from commercial sources at the highest purity available.

2.2. Plant materials

Plant specimens of *P. ferulacea*, *C. macropodum* and *H. persicum* were collected from Van region in Turkey, and were enumerated as F 11 175, F 11 176 and F 11 177, respectively. Samples were pressed, and dried according to herbarium techniques and identified by Flora of Turkey (Davis, 1972) and kept at the herbarium of Yüzüncü Yíl University (VANF).

2.3. Solvent extraction

Edible parts of plant samples were ground with Waring type stainless steel commercial blender. Chemical extraction was carried out in Heidolph Laborota 4000 rotary evaporator, overnight at 50 °C. Each time 10 g of the samples were extracted in methanol with a sample to solvent ratio of 1:10 (w/v). Extracts were then filtered through a double cheese cloth and dried under vacuum using a rotary evaporator.

2.4. Isolation of sheep liver microsomes

Sheep livers, bought from the slaughterhouse of Sincan, Ankara, were homogenized using glass-teflon homogenizer and centrifuged by Sorvall RC 5C Plus with SS-34 rotor at 10,800*g* for 25 min and Sorvall Combi Plus Ultracentrifuge at 133,573*g* for 50 min. The microsomes in the suspension containing 25–30 mg protein/ml were stored in Sanyo ultra-low freezer (−84 °C) up to three months (Iscan et al., 1998), and their protein content was measured with Lowry's method (Lowry, Rosebrough, Farr, & Randall, 1951).

2.5. Antioxidant activities of plant extracts

2.5.1. Lipid peroxidation inhibition evaluated by thiobarbituric acid test

Lipid peroxidation of the microsomes was induced by using 100 μM iron (II) solution. The end product of lipid peroxidation was quantified by determining the formed malondialdehyde (MDA). In acidic medium, MDA reacts with thiobarbituric acid (TBA) upon boiling and the resultant MDA–TBA adduct which has a pink colour absorbs at 532 nm. Formation of MDA–TBA adduct and all other TBA reactive substances (TBARS) was monitored by Cary 50 Bio UV–Vis spectrophotometer in the presence and absence of the extracts, and was expressed as nmol/mg of protein/min. The TBARS values were calculated using the extinction coefficient $1.56 \times 10^{-5}\,M^{-1}\,cm^{-1}$ (Heath & Packer, 1968). Percent inhibition of lipid peroxidation was calculated using the equation:

$$\% \text{ Inhibition} = [(A_0 - A_1)/A_0 \times 100]$$

where A_0 is the absorbance of control with ethanol and A_1 is the absorbance with the extract samples. 50% inhibitory concentration (IC_{50}) values were calculated after constructing the percent inhibition versus log (extract concentration) curve.

2.5.2. Free radical scavenging activity by DPPH method

The free radical scavenging activities were determined by DPPH method with some modifications of the method proposed by Blois (1958). A 0.05 mg/ml of DPPH ethanol solution which absorbs at 517 nm, produces approximately 1.3 U of absorbance. A series of extract solutions with varying concentrations were prepared by dissolving the dried extracts in ethanol and 0.1 ml of solutions from each extract was added to 1.4 ml of DPPH solution. The absorbance at 517 nm was recorded after 5 min of incubation at room temperature. Radical scavenging capacity of each extract has been calculated as the percent DPPH radical scavenging affect which is:

$$\text{DPPH Scavenging Effect } (\%) = [(A_0 - A_1)/A_0 \times 100]$$

where A_0 is the absorbance of the control with ethanol and A_1 is the absorbance of the sample in the presence of the extracts. IC_{50} concentrations were also calculated as explained above.

2.6. Determination of total phenolics content

Total concentration of phenolic compounds in extracts was determined using a series of gallic acid standard solutions (0.05–0.3 mg/ml) as in the method of Singleton and Rossi (1965), with some modifications. A 0.1 ml of each extract solution was mixed with 2 ml aqueous solution of 2% Na_2CO_3 and vortexed vigorously. The same procedure was also applied to the standard solutions of gallic acid. After 3 min, a 0.1 ml of 50% Folin–Ciocalteu's phenol reagent was added and each mixture were vortexed again. At the end of incubation for 30 min at room temperature, absorbance of each mixture was measured at 750 nm. Results were expressed as milligrams of total phenolics content per milligrams of extract as gallic acid equivalents (GAE).

2.7. Determination of sheep liver glutathione-S-transferase activity toward CDNB

GSTs activities were determined spectrophotometrically by monitoring the thioether formation at 340 nm using 1-chloro-2,4-dinitrobenzene (CDNB) as the substrate (Habig, Pabst, & Jakoby, 1974). Sheep liver cytosolic fractions were prepared used as the enzyme source to measure GST activity toward CDNB. Potassium phosphate buffer (0.2 M) and final 1 mM GSH was used throughout the experiments. Enzyme activities were carried out at 25 °C. Sheep liver microsomes (21 mg/ml) were used after 1/100 dilution with 10 mM potassium phosphate buffer, pH 6.0. Concentrations ranging between 0.2 and 2 mM CDNB were used as substrates The reactions started by the addition of the enzyme. Incubation mixtures without the enzyme source were used as blanks (non-enzymatic reactions). Enzyme activities with 10 µl of DMSO were regarded as control. The enzyme activities were expressed in terms of percent specific activity. One unit of GSTs activity is defined as the amount of enzyme producing µmol thioether per min. The kinetic constants K_m and V_{max} were determined for GST activity after Lineweaver–Burk plots were constructed. The enzyme activities were expressed in terms of percent specific activity. The extinction coefficient for CDNB conjugate at 340 nm is 0.0096 μM^{-1} cm^{-1} (Habig et al., 1974). Results were expressed as means ± SD and levels of significance were assessed using ANOVA test (analysis of variance) with 6–9 replicated measurements.

3. Results and discussion

3.1. Yield of plant extracts

Air dried samples (10 g) from aerial parts of each plant samples were extracted with 100 ml of methanol overnight at 50 °C. Percent yield of crude extracts following the removal of solvent using a rotary evaporator, were 4.18, 3.38, and 5.99 for *P. ferulacea*, *C. macropodum* and for *H. persicum*, respectively.

3.2. Antioxidant activities of plant extracts

Antioxidant activities of three plants from the same family were investigated by both DPPH scavenging and lipid peroxidation inhibition methods, and also their total phenolic contents were investigated.

DPPH percent scavenging activities of plant crude extracts were measured in different concentrations ranging between 0.01 and 1.4 mg/ml and results are given for DPPH percent radical scavenging activity (% RSA) versus extract concentrations in mg/ml in Fig. 1. IC_{50} values for DPPH percent scavenging activities of *P. ferulacea*, *C. macropodum* and *H. persicum* species were given in Table

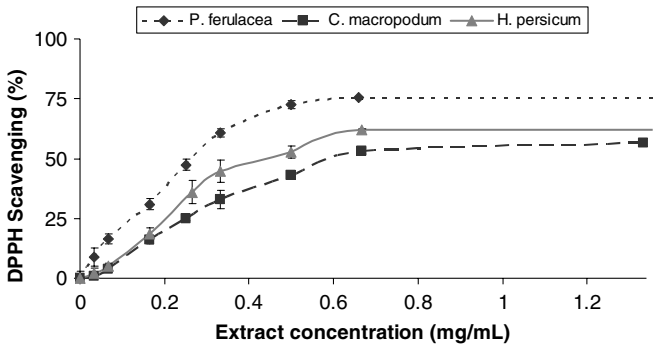


Fig. 1. DPPH scavenging activities of *Prangos ferulacea* (L.) Lindl, *Chaerophyllum macropodum* Boiss. and *Heracleum persicum* Desf. extracts.

Table 1
Comparison of 50% inhibition values of DPPH radical scavenging, lipid peroxidation and GST activity with the total phenolics contents of the extracts

Plants	DPPH scavenging IC_{50} (mg/ml)	LP inhibition IC_{50} (mg/ml)	GST inhibition IC_{50} (μg/ml)	TP GAEs μg/mg of extract
Prangos ferulacea	0.242	0.152	79.25	65.1 ± 6.4
Chaerophyllum macropodum	0.623	0.852	350.70	34.0 ± 7.0
Heracleum persicum	0.438	0.503	130.28	59.6 ± 2.8
Quercetin	0.0061	ND	ND	NA
α-Tocopherol	ND	0.23	ND	NA

DPPH scavenging IC_{50}: concentration of plant extracts for 50% of DPPH scavenging.
LP inhibition IC_{50}: concentrations of plant extracts for 50% inhibition of lipid peroxidation.
TP: total phenolics content μg equivalents of gallic acid/mg of plant extract.
GST inhibition IC_{50}: concentration of plant extracts for 50% inhibition of GST activity.
ND, not determined; NA, not applicable.

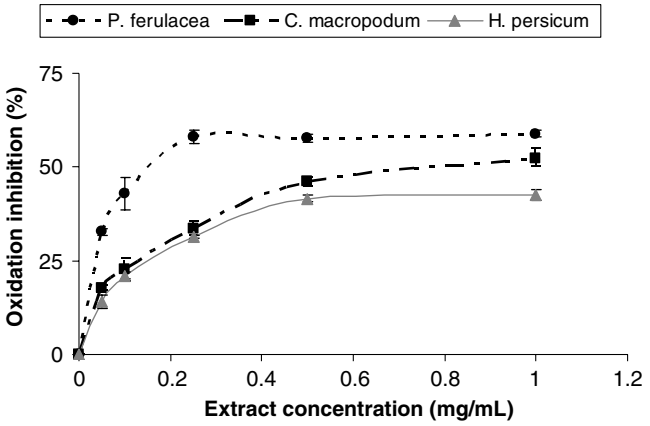


Fig. 2. Lipid peroxidation per cent inhibition data for *Prangos ferulacea* (L.) Lindl, *Chaerophyllum macropodum* Boiss. and *Heracleum persicum* Desf. extracts.

1, as calculated from the percent inhibition versus log concentration of extract curves.

Iron induced microsomal lipid peroxidation percent inhibitions by plant extracts were investigated using thiobarbituric acid test with 1 mg/ml sheep liver microsomes as the lipid source. Extracts were applied in concentrations varying between 0.05 and 1.0 mg/ml. Lipid peroxidation percent inhibition capacity of all the extracts are given in Fig. 2, against extract concentration in mg/ml. IC_{50} values of lipid peroxidation inhibitions for *P. ferulacea*, *C. macropodum* and *H. persicum* species are tabulated in Table 1.

3.3. Total phenolic contents

Total phenolic contents of plant extracts were determined by using gallic acid as standard as in the method of Singleton and Rossi (1965). The results were expressed as μg of total phenolics in mg of extract as GAE, as shown in Table 1. Among the plants studied, *P. ferulaceae* extract exerted the highest antioxidant activity as shown in the lipid peroxidation inhibition and DPPH radical scavenging capacities in Table 1. On the other hand, *C. macropodum* showed the lowest capacity among the three plants.

In this study, IC_{50} value of *P. ferulacea* extract for lipid peroxidation inhibition was found to be 0.152 mg/ml, which was more active comparing with the IC_{50} value 0.23 mg/ml of α-tocopherol as a standard. On the other hand, the same extract ($IC_{50} = 0.242$ mg/ml) was not quite as effective as standard quercetin ($IC_{50} = 0.0061$ mg/ml) in DPPH radical scavenging.

Our findings, 50% inhibitory concentrations given for DPPH radical scavenging and lipid peroxidation for *P. ferulacea* are consistent with those of Mavi, Terzi, Özgen, Yildirim, and Coşkun (2004), where the antioxidant activities of methanolic extract of *P. ferulacea* stems were given as IC_{50} of 0.201 mg/l for DPPH radical scavenging and IC_{50} of 0.228 mg/l for lipid peroxidation inhibition.

The amount of total phenolic compounds of methanolic extracts of *P. ferulacea* was determined as 65.1 μg per mg of crude extract, which is relatively higher than that reported in the literature (24 μg per mg of extract). In our study, all the aerial parts of the plant were included, however in the study of Mavi et al. (2004) the stem of *P. ferulacea* was used to prepare the crude extracts, which may contribute to the difference observed. Considerably high antioxidant activity of *P. ferulacea* extracts could be attributed to its content of various coumarins, alkaloids, flavonoids and terpenoids as reported by Sajjadi and Mehregan (2003).

Chaerophyllum macropodum extract displayed IC_{50} values of 0.623 mg/ml for DPPH and 0.852 mg/ml for lipid peroxidation inhibition which are significantly higher than the IC_{50} values of standards, quercetin and α-tocopherol as 0.0061 and 0.23 mg/ml, respectively . Hence, crude extract from the *C. macropodum* could be considered as the least effective antioxidant plant among the three plants studied. Total phenolics content of *C. macropodum* was also found to be very low with 34 μg of GAE in mg of extract, as expected to correlate with its low antioxidant capacity. In the literature, only information about *C. macropodum* was reported by Nematollahi, Akhgar, Larijani, Rustaiyan, and Masoudi (2005) related to its essential oil being rich in monoterpene hydrocarbons. This is the first and only study about the antioxidant capacity of *C. macropodum* and its total phenolics content.

Heracleum persicum extract with an IC_{50} value of 0.438 mg/ml for DPPH scavenging activity was the second effective antioxidant plant among others tested. Furthermore, lipid peroxidation inhibition effect of the extract was 0.503 mg/ml, which was comparable with its DPPH scavenging activity as expected. In the literature, preliminary phytochemical analysis of the *H. persicum* extracts showed the presence of alkaloids, terpenoids, triterpenes and steroids in the leaves (Mojab & Nickavar, 2003). Souri, Farsam, Sarkheil, and Ebadi (2004) reported the antioxidant components of *H. racleum persicum* fruits which were rich in furanocoumarins were also effective dermal photosensitizing agents and are widely used in the treatment of leukoderma and in suntan lotions (Aynehchi, Aliabadi, & Sormaghi, 1978).

3.4. Effects of plant extracts on glutathione-S-transferase activity

Regarding the importance of the role played by GST enzymes in multidrug resistance to chemotherapy, the interested plant extracts were also screened for their effects on GST activity besides their antioxidant efficiencies. All the extracts have shown considerable inhibition on the GST activity and the percent inhibition of GST enzyme was evaluated in the presence of varied extract concentrations (20–150 μg/ml). The results are plotted as the GST activity per cent inhibition in the presence of 100 μg/ml. of extract concentrations against the total phenolics contents for *P. ferulaceae*, *C. macropodum* and *H. persicum* as shown in Fig. 2. This is the first study on the three apiaceae extracts to evaluate their effect on total GST activity carried out in the sheep liver cytosol.

Comparing all the plant species for their IC_{50} values, *P. ferulaceae* was the most effective inhibitor of cytosolic GST activity toward CDNB, with a value of 79.25 μg/ml, followed by *H. persicum* (130.28 μg/ml) and *C. macropodum* (350.70 μg/ml). These results are in good correlation with the total phenolics contents of each extract (Fig. 3, Table 1). In the literature, the inhibitory effects of naturally occurring plant polyphenols such as tannic acid, ellagic acid, ferulic acid, caffeic acid, stilbene, quercetin, curcumin and chlorogenic acid against GST have long been reported by many researchers (Gyamfi et al., 2004; Kawabata et al., 2000). Quinines were also well-known examples of covalent inhibitors of GST enzymes (Zanden et al., 2003).

Our results have suggested that high GST inhibitory activity of plant extracts could be attributed to the high polyphenolic content, as indicated in the literature for the GST inhibitory effects of naturally occurring plant polyphenols. The GST activity of the cancer cells were also reported to be inhibited by the polyphenols (Zhang & Wong, 1997). The inhibitory effects of thonningianin A which was a novel antioxidant isolated from the medicinal herb, *Thonningia sanguinea* on uncharacterized rat liver

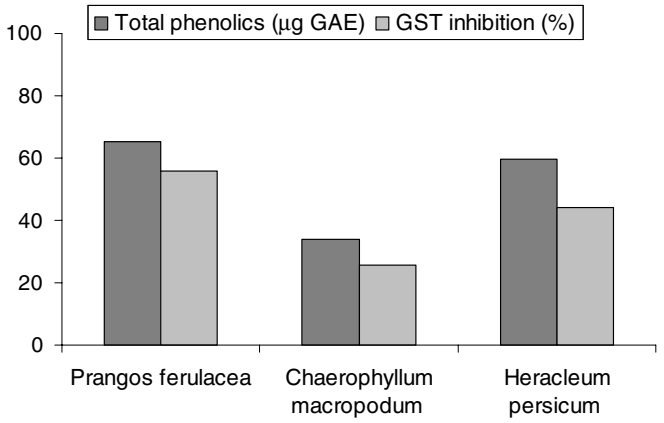


Fig. 3. GST inhibition plotted in the presence of plant extracts (100 μg/ml). Total Phenolic contents are expressed as μg GAEs per mg of extract.

GST and human GST P1-Th was also demonstrated and reported as a potent inhibitor of the conjugation of CDNB by crude cytosolic GSTs with an IC_{50} of 1.1 μM (Gyamfi et al., 2004).

Prangos ferulacea extract being the most effective inhibitor on crude cytosolic GST, was also important to evaluate its type of inhibition exerted on GST enzyme. The effect of *P. ferulacea* extract on crude cytosolic GST activity was determined by the kinetic study, carried out in the absence and presence of the extract. V_{max} for GST activity was measured in the presence of 50 μg/ml in the proximity of IC_{50} value of *P. ferulacea* extract. In the double reciprocal plot, *P. ferulacea* extract decreased the V_{max} of the enzyme from 2.8 to 1.49 μM/min/mg protein and K_m from 5.6×10^{-4} to 2.98×10^{-4} M. *P. ferulacea* extract decreased both the K_m and V_{max} values of the enzyme significantly. As a rule, when an inhibitor has a greater affinity for the enzyme-substrate complex than the free enzyme itself, the K_m decreases upon inhibitor binding, indicating a mixed type non-competitive inhibition. Consequently, *P. ferulacea* extracts has shown a mixed type non-competitive inhibition on crude cytosolic GST activity, as revealed in our observations.

4. Conclusions

Chaerophyllum macropodum, *Heracleum persicum* and *Prangos ferulacea* species, all belong to the same family of Apiaceae. When their antioxidant activities are compared, *P. ferulacea* is by far a better antioxidant than the others. Regarding to the importance of GST enzymes in cellular defence mechanisms and in multidrug resistance, selected plant extracts were evaluated for their effects on GST activity along with their antioxidant efficiencies. Among the plant extracts studied for GST inhibition activity, *P. ferulacea* was the most efficient inhibitor with IC_{50} value 79.25 μg/ml for GST, correlating with its high total phenolics content. *C. macropodum* and *H. persicum* were less effective antioxidants, however, they can still be considered as potential GST inhibitors.

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