Impact of maturity on phenolic composition and antioxidant activity of medicinally important leaves of *Ficus carica* L.

Muhammad Nadeem¹ · Alam Zeb¹

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Abstract *Ficus carica* L. is one of the oldest trees belonging to the mulberry family. It has both nutritional and medicinal benefits, as it is a source of potential bioactive compounds. Fig leaves were collected at four maturation stages, to evaluate the variation in polyphenolic compounds, antioxidant activity, and different pigments level. Polyphenols were identified using HPLC–DAD. Different pigments level, total phenolic contents, and radical scavenging activity were quantified. The HPLC analysis revealed the presence of fourteen polyphenolic compounds in the fig leaves. Quercetin-3-glucoside, caffeic acid, quercetin-3, 7-diglucoside, and coumaroyl-hexose were the major phenolic compounds. Kaempferol-3-O-sophorotrioside, cichoric acid and sinapic acid glucoside were identified for the first time. Significant quantitative changes were observed during maturation, particularly in polyphenolic compounds. There were significant changes in pigments level, total phenolic contents, and radical scavenging activity. It was observed that fig leaves are a rich source of polyphenolic compounds during all stages of maturation.

Keywords HPLC–DAD · Fig · Polyphenols · Antioxidants · Total phenolic contents

Introduction

The common fig (*Ficus carica* L.) is a deciduous, perennial tree belonging to the family *Moraceae*, which encompasses over 1400 species classified into about 40 genera (Baraket et al. 2009). It is one of the earliest cultivated crops worldwide and consumed in both dry and fresh form. Currently, the leading producers are Turkey, Egypt, Brazil, Spain, Greece, California, Morocco, Italy and regions with typically mild winters and hot dry summers (Tous and Ferguson 1996). The plant typically grows to about 18–20 feet. The stem is of moderate size with many scattering branches. Roots are underground and not adventitious. Stem and leaves contain milky white latex, which contains ficin, a protein-degrading enzyme. Figs leaves are largely green, petiolated, with curly margins, and have a hairy surface (Badgujar and Mahajan 2009). On maturation, the green fruit turns yellowish or red black. Seeds are smaller and edible. Ripe fruits can be eaten either fresh, dried, or in other stored form (Kamiloglu and Capanoglu 2015). Fig fruit contains carbohydrates, sugars, minerals, vitamins, organic acids, and phenolics acids, amino acids, low fats and phytosterol contents (Slatnar et al. 2011; Veberic et al. 2008). According to data of the mission variety of USDA, figs are the richest source of fiber, vitamin K, and minerals such as copper, manganese, magnesium, potassium, calcium, which are sufficient for human need (Vinson 1999). Phytochemicals studies have reported several compounds especially flavonoids and polyphenols and various other compounds like arabinose, β -amyrins, β -carotenes, glycosides, β -sitosterols and xanthotoxol (Jeong et al. 2009; Ross and Kasum 2002). The phenolic profile includes anthocyanins, phenolic acids, and flavones, while its leaves contain flavonoids, furanocoumarins and phenolic acids (Oliveira et al. 2012; Vallejo et al. 2012).

✉ Alam Zeb
Azebuom@gmail.com
Muhammad Nadeem
Biotechuum7@gmail.com

¹ Biochemistry Laboratory, Department of Biotechnology,
Faculty of Biological Sciences, University of Malakand,
Chakdara, KPK 18800, Pakistan

In folk medicine, figs have been used to cure several conditions like digestive, respiratory, inflammatory and cardiac disorders (Duke 2002). *Ficus carica* has also been reported to have antioxidant (Solomon et al. 2006), anti-HSV (Wang et al. 2004), antifungal (Aref et al. 2010) hemostatic (Richter et al. 2002), and hypoglycemic, anti-diabetic, anti-hyperlipidemic (Belguith-Hadriche et al. 2016), hepato-protective (Gond and Khadabadi 2008), immune responsive and radical scavenging activity (Yang et al. 2009). *Ficus* leaves possess anti-inflammatory and antioxidant activity (Ali et al. 2012), in vitro cytotoxic and anti-viral activity (Aref et al. 2011), hepato-protective (Aghel et al. 2011) and anti-diabetic properties (Irudayaraj et al. 2017). Belguith-Hadriche et al. (2016) showed that figs contain 28 pharmacologically important bioactive compounds. The presence of important bioactive compounds in the fig leaves, warranted us to determine their changes during growth. However, to the best of our knowledge, there are no data available on the composition of figs leaves and their changes during maturation. Hence, the present study was aimed to characterize and explore the changes in antioxidants, pigments, and polyphenols during maturation of figs leaves.

Materials and methods

Materials

All chemicals, solvents and reagents used were HPLC standard grade with purity higher than 99.7% and was purchased from Sigma-Aldrich (Germany). Ultra-pure deionized double distilled water was prepared with Labtech water still (Daihan Lab tech, South Korea) and then sonicated for 10 min.

Samples collection

Fig leaves were collected periodically (Table 1), from young fig trees (five random trees) in the northern region of KPK, Pakistan during April–May 2015. The leaves were

collected after sprouting reached the first 15 days. The leaves were then collected at the interval of 15 days based on the initial leaves growth. The collected leaves were dried in shade (20 ± 2 °C for 5 days). Dried samples were grinded into fine powder via a mechanical bender. For further analysis samples were made from the stored powdered materials.

Extraction of phenolic compounds

The powder sample (1 g) was extracted with water and methanol (40:60, v/v) for HPLC profiling. The mixture was heated for 1 h at 60 °C in a water bath. On cooling, the mixture was centrifuged at 4000 rpm for 10 min (Zeb 2015b). After centrifugation, 2 mL residue of each sample was filtered through Whatman filter paper and finally loaded into HPLC vials.

HPLC analysis of phenolic compounds

The phenolic profile of fig extract was quantified using an Agilent 1260 HPLC system (Agilent Technologies, Germany) with the basic parts like degasser, auto-sampler, quaternary pump and diode array detector (DAD). For phenolic analysis, the separation was achieved with a Zorbax Eclipse C18 column. The mobile phase consisted of solvent A (methanol: acetic acid: water: 10: 2: 88 v/v), and B (methanol: acetic acid: water 90: 2: 8 v/v) with the elution program as reported previously (Zeb 2015b). Elution time was 25 min. Phenolic compounds were analyzed using diode array detector at 280, 320 and 360 nm. Absorption spectra were recorded in 190–500 nm. Identification of phenolic compounds was based on the standard calibration curves of p-hydroxybenzoic acid, caffeic acid, caftaric acid, cichoric acid, and quercetin-3-glucoside and also tentatively done by comparing the absorption spectra with those in the literature.

Pigments contents

Chlorophylls content were analyzed and calculated as described previously with the help of UV–visible Pharamspec 1700 spectrophotometer (Shimadzu, Japan) (Zeb 2015a). The plant material (1 g) was extracted with 10 mL mixture of acetone and hexane (2:3, v/v). The samples were centrifuged at 10,000 rpm for 5 min. The absorbance of the supernatant was noted at 453, 505, 645 and 663 nm using a UV–visible Spectrophotometer. The values were expressed as mg/100 mL.

Table 1 Monthly weather report from April to May 2015 in the region of Talash District Dir KPK (www.accuweather.com)

Sample days	Date	Temperature (°C)	
		Highest	Lowest
15	01.04.2015	27	14
30	15.04.2015	30	17
45	30.04.2015	33	19
60	15.05.2015	36	21

Total phenolic contents

A colorimetric method, based on Folin–Ciocalteu reagent was used to determine the total phenolic contents (TPC) of the dried leave powder. Folin–Ciocalteu's reagent (0.2 N) and Na_2CO_3 (7.5%) was freshly prepared in the lab. Extract sample of 0.5 mL was mixed with 1 mL reagent and 0.5 mL Na_2CO_3 (7.5%) solution and reacted in dark for 1 h. Gallic acid served as the standard for preparing the calibration curve in the concentration range of 5–100 mg. The absorbance was noted at 510 nm. Total phenolic was stated as gallic acid equivalents (GAE) as reported recently (Zeb and Rahman 2017).

DPPH radical scavenging activity

DPPH radicals were used to quantify radical scavenging activity (RSA) of the extract. A fresh solution of DPPH was made in methanol at a concentration of 0.1 mM. Aliquot of 1.90 mL of DPPH solution from the stock was mixed with 10 μL of diluted sample and kept in dark for 30 min at room temperature (Zeb and Ullah 2017). The absorbance was noted at 515 nm against blank. The percentage of RSA was calculated using the equation: $\text{RSA} = (\text{Ac} - \text{As})/\text{Ac}$. Where Ac is the absorbance of control and As is the absorbance of the test sample (leaves).

Statistical analyses

All determinations were carried out three times. Data were evaluated via ANOVA and Tukey test at $\alpha = 0.05$ by using Graph Pad Prism 5 windows version 5.03 (Graph Pad Software Inc., 2009).

Results and discussion

Changes in the phenolic compounds

The changes in the phenolic composition during 15, 30, 45 and 60 days are shown respectively in Table 2. The level of p-hydroxybenzoic rapidly increased during first 30 days, and it slightly decreased until maturity but was higher than the initial values. This study is an agreement with Mahmood et al. (2012), who showed a similar trend of hydroxybenzoic acid during leaves maturation. The level of sinapic acid glucoside increased markedly from 0.54 to 1.14 mg/g at 60 days. Similarly, the same pattern of fluctuations was observed in gallic acid derivative level. The decline in their amount could be due to fact that gallic acid may change to tartaric acid esters form as maturation proceeds (Tian et al. 2009). While caffeic acid derivative

level was 1.32 mg/g at 30 days, but at later stages, it slightly increased till 60 days of maturation.

The level of coumaric acid derivative remained constant (0.88 and 0.89 mg/g) for 30 days and then slight increase occurred till maturation (1.19 mg/g) at 60 days. Mahmood et al. (2012) also have reported that coumaric acid level increases upon maturation in leaves. Our results correlated with the Butkhup et al. (2013), who reported that caffeic acid level declined as the maturation proceeds in fruit. At 15 days, the amount of caftaric acid was 43.66 mg/g, which was declined to 36.0 mg/g at 30 days of maturation. Increase in the caftaric acid occurred at 45 and 60 days respectively, however, the amount of caftaric acid was similar at both stages. Coumaroyl-hexose level sharply increased from 0.32 to 9.1 mg/g at 30 days, and then significant decline occurred with maturation. Similarly, quercetin-3,7-diglucoside level declined significantly at maturation of 30 days, while no significant changes were further observed till 60 days. Similarly, quercetin-3-triglucoside level which was 8.96 mg/g, sharply declined to 1.74 mg/g at 30 days and increased to the maximum level of 9.05 mg/g at maturation. The quercetin-3-glucoside amount showed in this study was lower as compared to the previously reported values (Oliveira et al. 2009). In a previous study, Vaya and Mahmood (2006) has also reported that quercetin is the major flavonoid in figs, which is in agreement with this study. Cichoric acid level slightly increased until maturation. At 30 days, the level of quercetin-3-glucoside increased sharply, but later till maturation, it declined significantly. The quercetin-3-glucoside level was sharply increased at 30 days, but at later maturation stages, decline occurred. Similar trend in the composition of quercetin-3-glucoside was also observed in apricot leaves duration maturation (Zeb et al. 2017), suggesting that this compound may follow similar trend during maturation in plant trees. The kaempferol-3-sophorotrioside level was markedly increased from 0.16 to 1.11 mg/g at maturation of 60 days, doubled than the amount present in 15 days of maturation. The amount of kaempferol present in this study shows correlation with the previous study of Miletić et al. (2014). These results showed that significant variations occurred in the phenolic composition of fig leaves during maturation at the selected duration. Some of the identified compounds (peak 1, 4, 6, 9, and 13) were higher at 30 days of maturation, thus, this period may be selected for obtaining the choice of compound (Fig. 1).

Changes in pigments contents

In plants, pigments are physiologically important, it provides protection against light and oxygen. Chlorophyll is the green pigment that is responsible for photosynthesis,

Table 2 Characteristics and composition of phenolic compounds during different maturation stages of *Ficus carica* leaves

Peak No.	Compound	Peak Characteristics		Composition (mg/g DW)*			
		λ_{max} (nm)	Purity (%)	15 days	30 days	45 days	60 days
1	P-hydroxybenzoic acid	256	99.2	2.15 $\pm$ 0.02a	3.76 $\pm$ 0.01b	3.16 $\pm$ 0.05c	2.82 $\pm$ 0.02d
2	Sinapic acid glucoside	328	99.5	0.54 $\pm$ 0.07a	0.79 $\pm$ 0.02b	1.03 $\pm$ 0.01c	1.14 $\pm$ 0.03d
3	Gallic acid derivative	279	99.4	1.06 $\pm$ 0.05a	1.51 $\pm$ 0.03b	1.61 $\pm$ 0.05c	1.21 $\pm$ 0.04d
4	Caffeic acid derivative	315, 287	99.1	1.32 $\pm$ 0.02a	2.64 $\pm$ 0.04b	1.88 $\pm$ 0.09c	2.11 $\pm$ 0.08c
5	Coumaric acid derivative	312	99.5	0.89 $\pm$ 0.02a	0.89 $\pm$ 0.03a	1.21 $\pm$ 0.1b	1.19 $\pm$ 0.1b
6	Caffeic acid	323, 298sh, 238	99.6	2.59 $\pm$ 0.07a	2.27 $\pm$ 0.09b	2.15 $\pm$ 0.08b	1.59 $\pm$ 0.02c
7	Pro-anthocynidin B1	310, 286	99.7	0.54 $\pm$ 0.02a	0.77 $\pm$ 0.03b	0.93 $\pm$ 0.04c	0.82 $\pm$ 0.07b
8	Caftaric acid	328, 298, 242	99.6	43.7 $\pm$ 0.8a	36.0 $\pm$ 0.1b	38.7 $\pm$ 0.2c	38.5 $\pm$ 0.2c
9	Courmaroyl-hexose	314, 233	99.6	0.32 $\pm$ 0.01a	9.1 $\pm$ 0.04b	3.83 $\pm$ 0.01c	4.67 $\pm$ 0.04d
10	Quercetin -3,7-diglucoside	332, 268	99.5	13.9 $\pm$ 0.02a	9.58 $\pm$ 0.05b	10.3 $\pm$ 0.03c	9.88 $\pm$ 0.03b
11	Quercetin -3-triglucoside	338, 271	99.1	8.96 $\pm$ 0.04a	1.74 $\pm$ 0.02b	9.88 $\pm$ 0.05a	9.05 $\pm$ 0.01c
12	Cichoric acid	328, 298sh, 244	99.2	1.42 $\pm$ 0.03a	1.32 $\pm$ 0.01b	1.71 $\pm$ 0.01c	1.51 $\pm$ 0.04a
13	Quercetin-3-glucoside	354, 256	99.3	3.48 $\pm$ 0.05a	7.12 $\pm$ 0.01b	5.57 $\pm$ 0.1c	6.12 $\pm$ 0.1c
14	Kaempferol-3-O-soprotrioside	347, 295sh, 265	99.7	0.16 $\pm$ 0.07a	0.82 $\pm$ 0.03b	0.88 $\pm$ 0.04b	1.11 $\pm$ 0.01c

*Values are means with standard deviation of triplicate measurements. Different letters (a-d) in the same compound represent significance at $p < 0.05$ (Tukey test) with respect to maturation days

Fig. 1 Representative HPLC–DAD chromatograms at 320 nm of the fig leaves during 15, 30, 45 and 60 days of maturation. Details characteristics of each peak is given in Table 2

carotenoids provide distinctive bright colors. The chlorophyll *a* level was higher than chlorophyll *b* (Fig. 2). The

amount of chlorophyll *a* increased significantly ($p < 0.05$) during all maturation stages, with highest amounts at

Fig. 2 Changes in the amounts of chlorophyll *a* and *b* during leaves maturity. Different letters *a–d* in each case is significantly ($p < 0.05$) different

60 days. The increase in the chlorophyll *a* may be due to the increased potential of the leaf for photosynthesis supported by the leaf size. Similarly, chlorophyll *b* level also increased during first 30 days but remained constant until 60 days, where it increased significantly. The difference in the changes of both chlorophylls may be due to the absence of specific light during the April–May or any other seasonal variation. Sabir et al. (2010) reported that young leaves contain high chlorophyll contents, which may be correlated with iron level, which represents the importance of iron in chlorophyll. The β -carotene level decreased significantly ($p < 0.05$) at 30 days, while significant increase occurred at 45 and 60 days of maturation (Fig. 3). Similarly, lycopene amount significantly decreased with respect to maturation stage of 30 and 45 days, and significantly increased at 60 days of maturation. This study is in accordance with previous studies (Abushita et al. 1997;

Fig. 3 Changes in the amounts of β -carotene and lycopene during leaves maturity. Different letters *a–d* in each case is significantly ($p < 0.05$) different

Kotikova et al. 2009), which reported that β -carotene and lycopene level increases with maturation in the fruit of tomatoes. The higher amount of lycopene is linked with chlorophyll *a*, confirming the correlation between lycopene and chlorophyll *a* (Arias et al. 2001).

Changes in TPC and radical scavenging activity

Phenols are class of secondary metabolites, having several therapeutic activities, both in animal and plants (Angelino et al. 2017). These compounds have the ability to quench free radicals because of their hydrogen donating potential and antioxidant activity, thus reducing oxidative stress (Zeb 2018) during growth or maturation. The total phenolic contents were maximum at 15 days and no significant variations were observed at 15 and 30 days of the collection, but a significant decline ($p < 0.05$) at 60 days was noted. Similar results were also reported by Morelló et al. (2005), who showed that phenolic contents decreased as maturation proceeds in olive drupes. The RSA value was increased at 15 days, but no significant changes occurred during later maturation stages (Fig. 4). Similar results were also reported by Duda-Chodak et al. (2011) in apple fruit, a maturation that antioxidant and phenols contents decrease

Fig. 4 Changes in total phenolic contents and radical scavenging activity during leaves maturity. Different letters *a–b* in each case is significantly ($p < 0.05$) different

as maturation proceeds. Our results are in contrast to Crisosto et al. (2010) who reported that fig fruit antioxidant activity does not change upon maturity. In our study, a strong correlation was found between antioxidant activity and total phenolics contents which are in contrast to Pedisić et al. (2007). Similarly, there were strong correlations ($r^2 = 0.9034$ and 0.8282) observed between β -carotene with chlorophyll a and b, respectively. This showed that during the development of leaf, antioxidant activity increases as photosynthetic ability increases. The HPLC phenolic profile also showed a decrease in the phenolic compounds. However, the total phenolic compounds determined using HPLC were higher than using spectroscopic method, representing the sensitivity of the HPLC method.

Conclusion

The HPLC results revealed the presence of fourteen polyphenolic compounds in fig leaves collected from KPK, Pakistan. They were p-hydroxybenzoic acid, sinapic acid glucoside, gallic acid derivative, caffeic acid derivative, coumaric acid derivative, caffeic acid, pro-anthocyanidin B1, caftaric acid, coumaroyl-hexose, quercetin-3,7-diglucoside, quercetin-3-triglucoside, cichoric acid, quercetin-3-glucoside, and kaempferol-3-O-sophorotrioside. Our study confirmed significant changes in the major polyphenolic compounds depending on the leaves maturity. Moreover, our results also showed significant variations in the content of pigments, total phenols, and RSA during maturation. It was observed that fig leaves are a rich source of polyphenolic compounds during 45 and 60 days of maturation.

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Compliance with ethical standards

Conflict of interest None.

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