5-2024

PHENOLIC COMPOUNDS IN DATE FRUITS (Phoenix dactylifera L.)

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UAEU
جامعة الإمارات العربية المتحدة
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DOCTORATE DISSERTATION NO. 2024: 42

College of Agriculture and Veterinary Medicine

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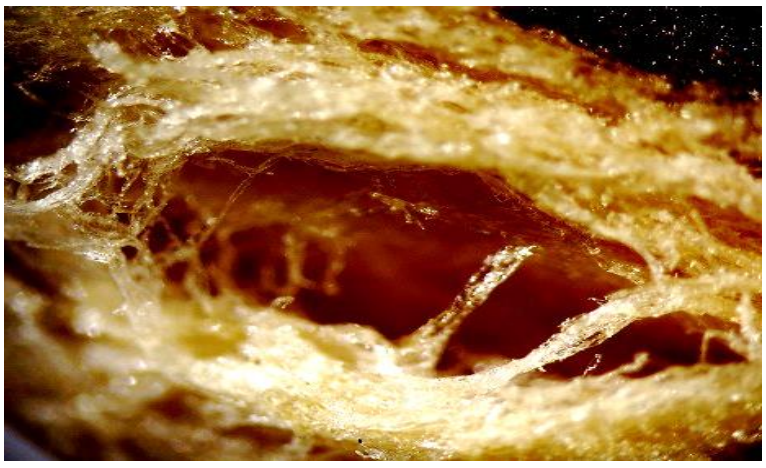

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This dissertation is submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Food Science and Technology

May 2024

United Arab Emirates University Doctorate Dissertation
2024: 42

Cover: Image of Date fruit
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Print: University Print Service, UAEU 2024

Declaration of Original Work

I, Muneeba Zubair Alam, the undersigned, a graduate student at the United Arab Emirates University (UAEU), and the author of this dissertation entitled "*Phenolic Compounds in Date Fruits (Phoenix dactylifera* L.*)*," hereby solemnly declare this is the original research work done by me under the supervision of Prof. Afaf Kamal-Eldin, in the College of Agriculture and Veterinary Medicine at UAEU. This work has not previously formed the basis for the award of any academic degree, diploma, or similar title at this or any other university. Any materials borrowed from other sources (whether published or unpublished) and relied upon or included in this dissertation have been properly cited and acknowledged in accordance with appropriate academic conventions. I further declare that there is no potential conflict of interest concerning this dissertation's research, data collection, authorship, presentation, and publication.

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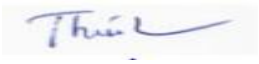
   Signature  Date 23 May 2024

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Abstract

This study investigated the phenolic compounds in date fruits, mainly soluble and hydrolyzable compounds, and insoluble melanin. Soluble (27.5–54.0 mg/100 g FW) and hydrolyzable (24.0–78.5 mg/100g FW) phenolic compounds were determined in 18 cultivars using ultra-performance liquid chromatography coupled with mass spectrometry. Phenolic acids were predominant in both fractions while flavonoids were mainly present in the soluble phenolic fraction and the proanthocyanidin B_1 and B_2 were only present in the hydrolyzable fraction. Four total antioxidant activity assays (total phenolic content, ABTS, FRAP, and DPPH) gave different results for both the soluble and hydrolyzable fractions of 26 date fruit cultivars, which questions the reliability of these assays. Date fruits contained high levels of insoluble allomelanin (1.2–5.1 g/100 g FW). Electron paramagnetic and nuclear magnetic resonance coupled with computational density functional theory suggested that the date fruits melanin is based on (-) -epicatechin stacked oligomers. Overall, this study provides new insights into the phenolic compounds present in date fruits, particularly hydrolyzable phenolic compounds and melanin.

Keywords: Date fruits, *Phoenix dactylifera* L., hydrolyzable phenolic compounds, melanin.

Title and Abstract (in Arabic)

المركبات الفينولية في ثمار التمر (*Phoenix dactylifera* L.)

الملخص

تبحث هذه الدراسة في المركبات الفينولية في ثمار التمر، وخاصة المركبات الفينولية غيرالقابلة للذوبان. استخدمت الدراسة التحليل السائل فائق الأداء إلى جانب تحليل قياس الطيف الكتلي في فصل هذه المركبات وتعريفها وتحديد كمياتها. كما استكشفت الدراسة التوافق بين هذه الطريقة وطرق تحليل مضادات الأكسدة الكلية للمستخلصات القابلة وغير القابلة للذوبان. كما اشتملت الدراسة على تحديد نسبة الميلانين وصفاته الكيميائية. كشفت نتائج الدراسة أن ثمار التمر تحتوي على محتوى فينولي عالى ولكنه متفاوت بين الأصناف التي تمت دراستها وأن المركبات الفينولية التي تذوب بعد المعالجة القلوية موجودة بكميلت متساوية مع المركبات القابلة للذوبان. المركبات الفينولية البارزة التي تم تحديدها هي حمض الغال وحمض الفيروليك واللوتولين والكيرسيتين. يحتوي المستخلص غير الذائب على بروانثوسيانيدينس (B1 و B2). وقد تم اكتشاف الميلانين، وهو مركب نشط بيولوجيا، في أصناف ثمار التمر لأول مرة. اشارت دراسات الرنين المغنطيسي الإلكتروني والنووى إلى أن الميلانين المشتق من ثمار التمر يحتوي على أوليغومرات تعتمد على مركب epicatechin. بشكل عام، تقدم هذه الدراسة رؤى جديدة حول المركبات الفينولية الموجودة في ثمار التمر، وخاصة المركبات الفينولية غير الذائبة والميلانينالسرطاني مع الإحتفاظ باكبر قدر من خلايا المناعة السليمة و انسجة الجسم المحيطة بالورم.

مفاهيم البحث الرئيسية: ثمار التمر، *Phoenix dactylifera* L.، المركبات الفينولية غير القابلة للذوبان، الميلانين.

List of Publications

This dissertation is based on the work presented in the following papers, referred to by Roman numerals.

I. Alam, M. Z., Fristedt, R., Landberg, R., & Kamal-Eldin, A. (2024). Soluble and hydrolyzable phenolic compounds in date fruits (*Phoenix dactylifera* L.) by UPLC-QTOF-MS/MS and UPLC-DAD. *Journal of Food Composition and Analysis*, *132*, 106354. https://doi.org/10.1016/J.JFCA.2024.106354

II. Alam, M. Z., Alhebsi, M. S. R., Ghnimi, S., & Kamal-Eldin, A. (2021). Inability of total antioxidant activity assays to accurately assess the phenolic compounds of date palm fruit (*Phoenix dactylifera* L.). *NFS Journal*, *22*, 32–40. https://doi.org/10.1016/j.nfs.2021.01.001

III. Alam, M. Z., Ramachandran, T., Antony, A., Hamed, F., Ayyash, M., & Kamal-Eldin, A. (2022). Melanin is a plenteous bioactive phenolic compound in date fruits (*Phoenix dactylifera* L.). *Scientific Reports*, *12*, 6614. https://doi.org/10.1038/s41598-022-10546-9

IV. Alam, M. Z., Okonkwo, C. E., Cachaneski-Lopes, J. P., Graeff, C. F. O., Batagin-Neto, A., Tariq, S., Varghese, S., O'Connor, M. J., Albadri, A. E., Webber, J. B. W., Tarique, M., Ayyash, M., & Kamal-Eldin, A. (2024). Date fruit melanin is primarily based on (−)-epicatechin proanthocyanidin oligomers. *Scientific Reports*, *14*(1), 1–12. https://doi.org/10.1038/s41598-024-55467-x

Author's Contribution

The contribution of Muneeba Zubair Alam to the papers included in this dissertation was as follows:

I. Contributed to the investigation and writing of the original draft.

II. Data curation, visualization, and formal analysis of the data.

Author Profile

Muneeba Zubair Alam is a PhD candidate at United Arab Emirates University (UAEU) in Al-Ain, UAE. She received her B.Sc. and M.Phil. in Food Science and Technology from the University of Karachi, Pakistan, in 2009 and 2013, respectively. During her PhD studies at UAEU, she also worked in the research lab at Chalmers University of Technology in Sweden for six months (February-August 2022).

Acknowledgments

It’s my pleasure to acknowledge the roles of several individuals who were instrumental in completing my Ph.D. research. I would like to express my sincere gratitude to my advisor, Professor Afaf Kamal-Eldin, for her invaluable guidance and support throughout my PhD journey. Her expertise was instrumental in shaping the direction of my research and refining my work. Her unwavering encouragement, insightful feedback, and critical analysis of each draft proved to be an invaluable source of strength during the triumphs and challenges of this PhD journey.

I thank my advisory committee, Professor Mutamed Ayyash, and Professor Habiba Ali, for their guidance, support, and assistance throughout my Ph.D. journey. I thank Professor Rikard Landberg for supporting and connecting me with valuable resources during my research stay at Chalmers University of Technology, Sweden. Thank you, Rikard Fridiest, for your patience with my questions and for allowing me to refine my research project confidently. I thank all the co-authors of my publications; I consider myself fortunate to have collaborated with them, as their contributions have substantially enhanced my research.

I would like to thank all the faculty members, instructors, and laboratory specialists for their help and support during my PhD work at the Department of Food Science. I also want to sincerely thank my friends for supporting and motivating me during this academic journey. I would also like to thank the UAEU research office for the funding. Special thanks to my family members; this PhD would not have been possible without their support. They helped me mentally and emotionally throughout this long journey.

Dedication

To my beloved parents and family

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AAE	Ascorbic acid equivalent
ABTS	2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
ACE	Angiotensin-converting enzyme
AE	Antiradical efficiency
AEAC	Ascorbic acid equivalent's antioxidant capacity
ANR	Anthocyanidin reductase
ANS	Anthocyanidin synthase
BA4H	Benzoic acid 4-hydroxylase
C4H	Cinnamate 4-hydroxylase
CE / CEQ	(+) - Catechin equivalent
CHI	Chalcone isomerase
CHS	Chalcone synthase
COMT	Caffeoylshikimate esterase
C^{13} NMR	Carbon-13 Nuclear magnetic resonance
CYT	Cytochrome
CTC	Condensed tannin content
CYG	Cyanidin 3-glucoside equivalents
DAD	Diode array detector
DFR	Dihydroflavonol reductase
DPPH	2-diphenyl-1- picrylhydrazyl
EC_{50}	Half maximal effective concentration
ECH	Enoyl-CoA hydratase/aldolase
EPR	Electron paramagnetic resonance
ESI	Electron spray ionization

F3H	Flavanone 3-hydroxylase
FAE	Ferulic acid equivalent
FCS	trans-feruloyl-CoA
FGT	Flavonoid glycosyltransferase
FLS	Flavanol synthase
FNS	Flavone synthase
FRAP	Ferric reducing antioxidant power
GAE	Gallic acid equivalent
GC	Gas chromatography
GT	Glucosyltransferase
H^1NMR	Proton nuclear magnetic resonance
HCT	Hydroxycinnamoyl transferase
HPLC	High-performance liquid chromatography
IC_{50}	Half-maximal inhibitory concentration
LC	Liquid chromatography, Laccase
MALDI	Matrix-assisted laser desorption/ionization
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
OD	Optical density
ORAC	Oxygen radical absorbance capacity
PAD	Phenolic acid decarboxylase
PAL	Phenylalanine ammonia lyase
PC5H	Protocatechuic acid 5 hydroxylase
PCA	Principal component analysis
PDA	Photodiode array detector
PLS	Partial least regression

POD	Peroxidase
PPO	Polyphenol oxidase
QE	Quercetin equivalent
GC	Gas chromatography
QTOF	Quadrupole time of flight
REQ / RE	Rutin Equivalent
RT	Retention time
SRSA	Superoxide radical scavenging ability
TCT	Total condensed Tannins
TE	Trolox equivalent
TEAC	Trolox equivalent antioxidant capacity
TFC	Total flavonoid content
TFOC	Total flavonol content
TOF	Time of flight
TPC	Total phenolic content
UAE	United Arab Emirates
UFGT	Flavonoid-3-O-glucoyltransferase
UHPLC	Ultra-high-performance liquid chromatography
UPLC	Ultra-performance liquid chromatography
UV	Ultraviolet
VCE	Vitamin C equivalents
VDH	Vanillin dehydrogenase

Chapter 1: Introduction

1.1 Overview

Date fruits (*Phoenix dactylifera* L.) are considered a staple diet in all Arab nations, offering a wealth of potential health benefits and serving as a major source of nutrients (Hammami et al., 2023). Date fruits are rich sources of phenolic compounds (El Hadrami & Al-Khayri, 2012). The Arab world leads in date production, with 160 million palm trees producing more than 77% of the global output annually (FAO and AOAD, 2023). The United Arab Emirates (UAE) is among the top 10 date palm producers, with 40 million trees, producing 323,478 metric tons of dates in 2019 (UAEU, 2022).

Plant foods, including fruits, vegetables, cereal grains, and legumes, are major sources of phenolic compounds in the human diet (Rudrapal et al., 2022). Over the past decades, an increase in awareness and knowledge has been observed among consumers regarding the health benefits of phenolic compounds (Brennan, 2024). These compounds can protect the body from various ailments, such as cancer, heart disease, hyperlipidemia, and nerve damage, by functioning as antioxidants, anti-inflammatory agents, and signaling molecules (Haminiuk et al., 2012). Phenolic compounds in plant foods exist in soluble, hydrolyzable (esters or glycoside conjugates), and insoluble forms (Shahidi & Hossain, 2023). Because of the distribution of phenolic compounds across different plant tissues, their cellular and subcellular levels are not always similar. Soluble phenolic compounds are present within plant cell vacuoles, whereas hydrolyzable phenolic compounds exist in cell walls. Phenolic compounds have complex structures ranging from simple to highly polymerized compounds. Given their complex nature, the extraction of phenolic compounds from their natural sources is complex. Besides their structures, the food matrix may substantially hinder their maximum recovery. Moreover, complexes with protein, fiber, or other elements may hinder the complete extraction of some phenolic compounds (Shahidi & Hossain, 2023). The effect of the structure of these compounds on their extractability should be thoroughly understood to take full advantage of their various applications. In addition, specific compounds must be identified using cutting-edge methods, such as nuclear magnetic resonance (NMR) and mass spectroscopy. The

polyphenolic content of foods is greatly influenced by environmental factors, including soil type, sun exposure, and rainfall (Alam et al., 2023; Rajbhar et al., 2015).

1.2 Research Questions and Scope of the Dissertation

Previous studies on the phenolic composition of date fruits were highly limited to those that are extractable in aqueous organic solvents, i.e. soluble phenols. Al-Farsi et al. (2005) used alkaline hydrolysis to release esterified phenolic acids and quantified them using high-performance liquid chromatography (HPLC). However, no profiling has been conducted on the other hydrolyzable phenolic compounds or the presence of insoluble phenolic compounds in date fruits. Total antioxidant activity methods were widely used in the study of phenolic compounds in date fruits, but their validity/reliability has not been investigated. This thesis aimed to answer the following questions:

What are the different phenolic compounds (soluble, hydrolyzable, and insoluble) in date fruits?

What is the variability in phenolic compound concentrations in wide collections of cultivars?

How reliable are the total antioxidant assays, e.g. TPC, ABTS, FRAP, and DPPH, in estimating the phenolic contents in dates?

1.3 Research Objectives

The specific aims of this study were to:

- identify and quantify phenolic compounds in soluble and hydrolyzable extracts using UPLC-QTOF-MS/MS and UPLC-DAD.
- evaluate the total antioxidant activities of the soluble and hydrolyzable phenolic compounds using total phenolic content (TPC), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), ferric reducing antioxidant power (FRAP), and 2-diphenyl-1-picrylhydrazyl (DPPH) assays.
- quantify melanin in date fruits and study its physiochemical characteristics.

1.4.1 Phenolic Compounds

Phenolic compounds, which are widely distributed in the plant kingdom, represent the most investigated phytochemicals because of their anticipated health-promoting effects and wide industrial applications in various fields, such as foods, cosmetics, and pharmaceuticals (Nurzyńska-Wierdak, 2023). The primary edible sources of phenolic compounds are fruits, vegetables, seeds, cereals, beverages (e.g., wine, tea, and juices), and spices. Phenolic compounds are divided into different classes, each with distinct structures and functions. Figures 1 show the main classes of phenolic compounds and their building blocks and Figure 2 presents examples of common phenolic compounds in foods.

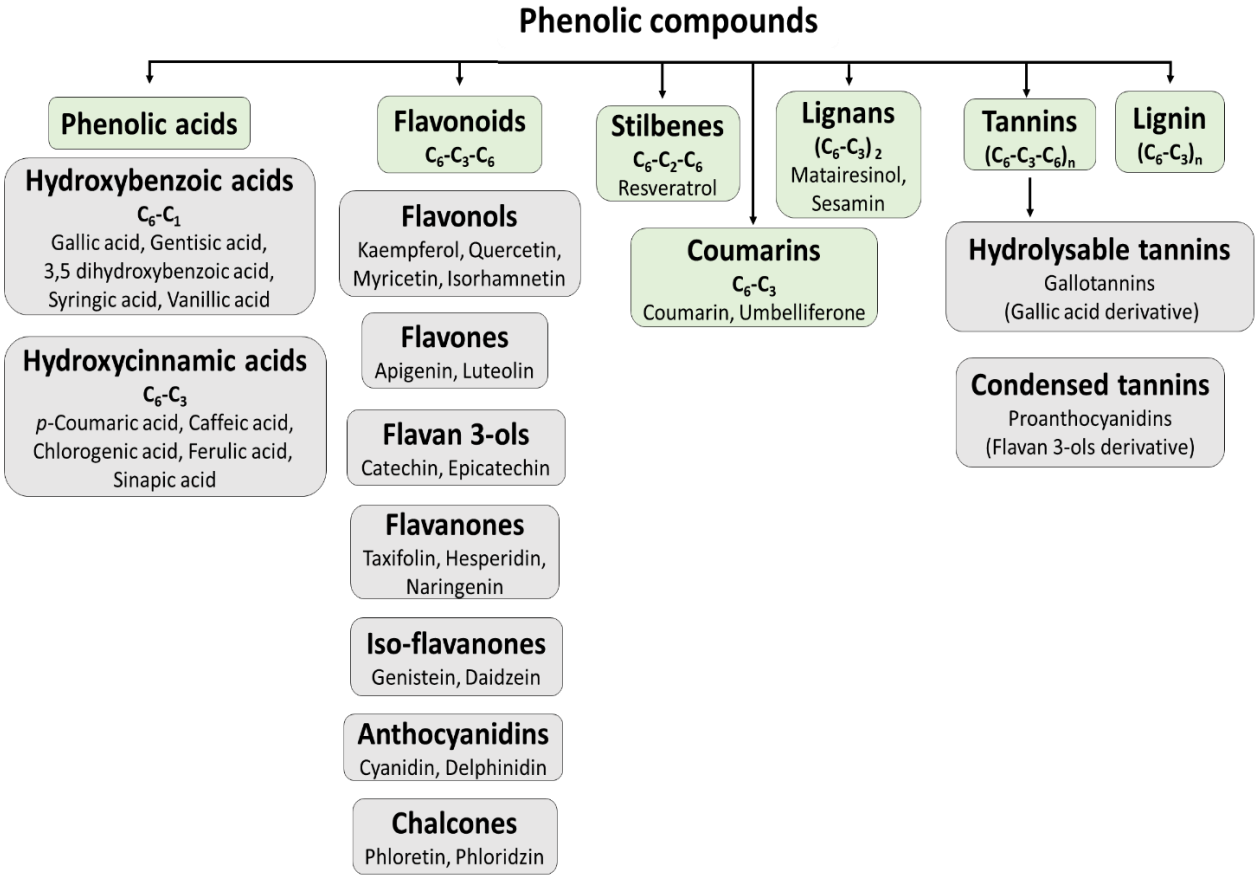

Figure 1: Classification of phenolic compounds (Zhang et al., 2022).

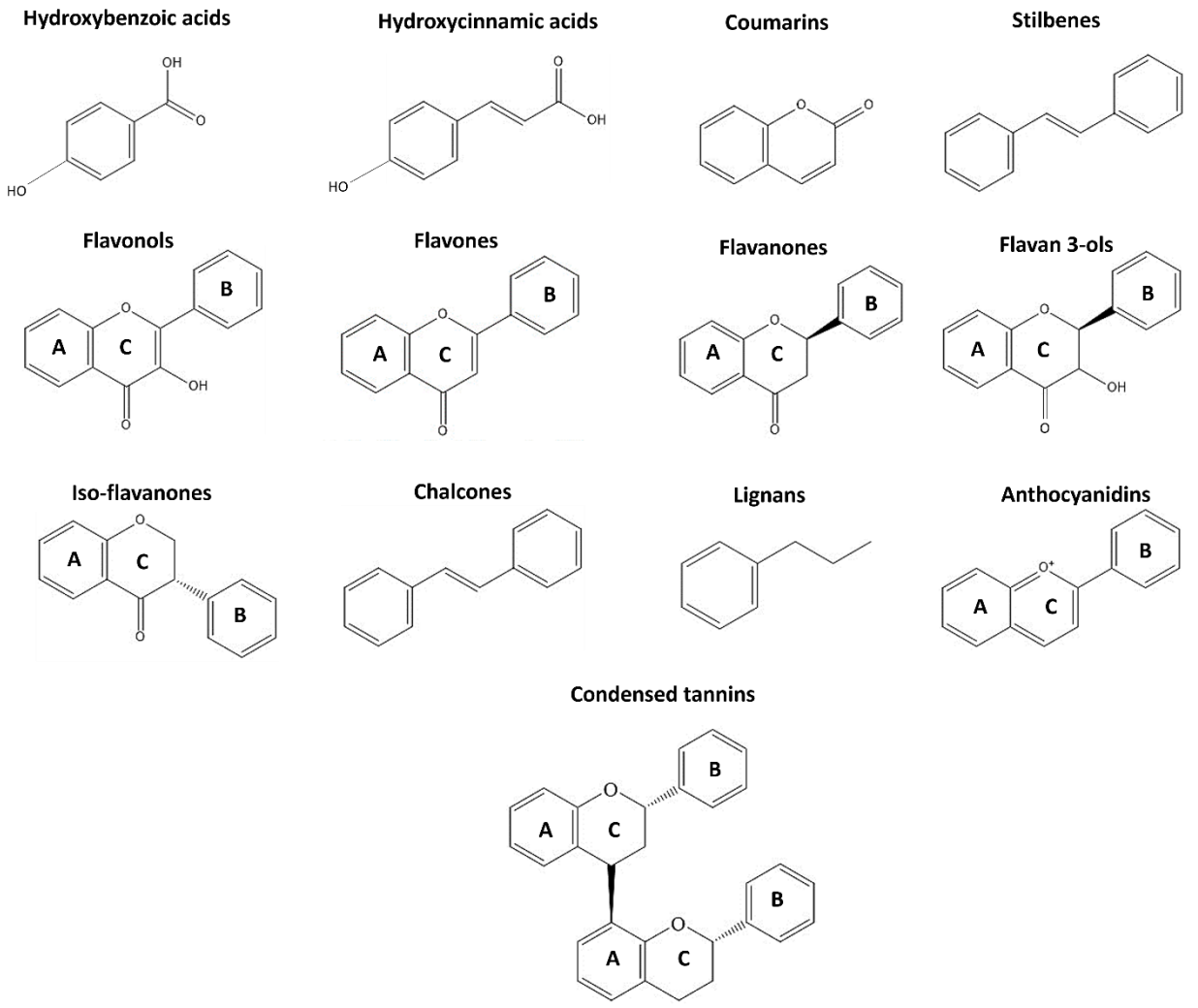

Figure 2: Basic structures of selected phenolic classes.

Phenolic compounds are produced by the phenylpropanoid pathway (Figure 3) and contribute to fruit pigmentation and disease resistance during ripening (Singh et al., 2010; Marchiosi et al., 2020). Phosphoenolpyruvate undergoes several reactions to form chorismic acid, which is converted into phenylalanine. The first crucial regulatory step is the deamination of phenylalanine to form cinnamic acid, which is catalyzed by the enzyme phenylalanine ammonia-lyase (PAL). In the following step, cinnamic acid undergoes two processes to synthesize hydroxybenzoic and hydroxycinnamic acids. The action of cinnamate 4-hydroxylase (C4H) to produce *p*-coumaric acid is essential for the synthesis of other hydroxycinnamic acids (caffeic, ferulic, and chlorogenic acids). The flavonoid biosynthesis begins with the formation of *p*-coumaroyl-CoA, which reacts with malonyl-CO to generate chalcone with the basic skeleton of C_6-C_3-C_6 (Liu et al., 2021). Various

plants and plant parts exhibit differences in their phenolic composition, influenced by genetics and environmental conditions that affect the activity of enzymes, such as hydroxylases, reductases, and isomerases (Hazzouri et al., 2015; Alam et al., 2023). Flavanone 3-hydroxylase (F3H) or flavonol synthase (FLS) is the key enzyme in the central pathway, which converts flavanone to dihydroflavonols. Dihydroflavonols undergo two different pathways, namely, flavanol synthesis through the action of FLS and the production of leucoanthocyanidins, which are precursors of anthocyanidins and proanthocyanidins (Rehan, 2021). Anthocyanidins undergo glycosylation *via* the activation of flavonoid-3-O-glucosyltransferase (UFGT), producing anthocyanins, which are generally more stable than their aglycone forms. The oligomeric proanthocyanidins undergo further polymerization reactions to form polymeric proanthocyanidins and melanin. The enzymes and mechanisms in these condensation and polymerization reactions remain unknown (Yu et al., 2023).

Various compounds, such as anthocyanins, flavones, flavonols, and carotenoids, are responsible for colors in plant foods (Lu et al., 2021). Pigments arising from different enzymatic and nonenzymatic processes are also responsible for colors, including melanoidins from the Maillard reaction, caramels, and melanin formed through enzymatic polyphenol oxidase (PPO) processes (Al-Amrani et al., 2020; Daas Amiour & Hambaba, 2016). Pigment changes and their associated phenolic compounds are expected to influence fruit color and antioxidant potential.

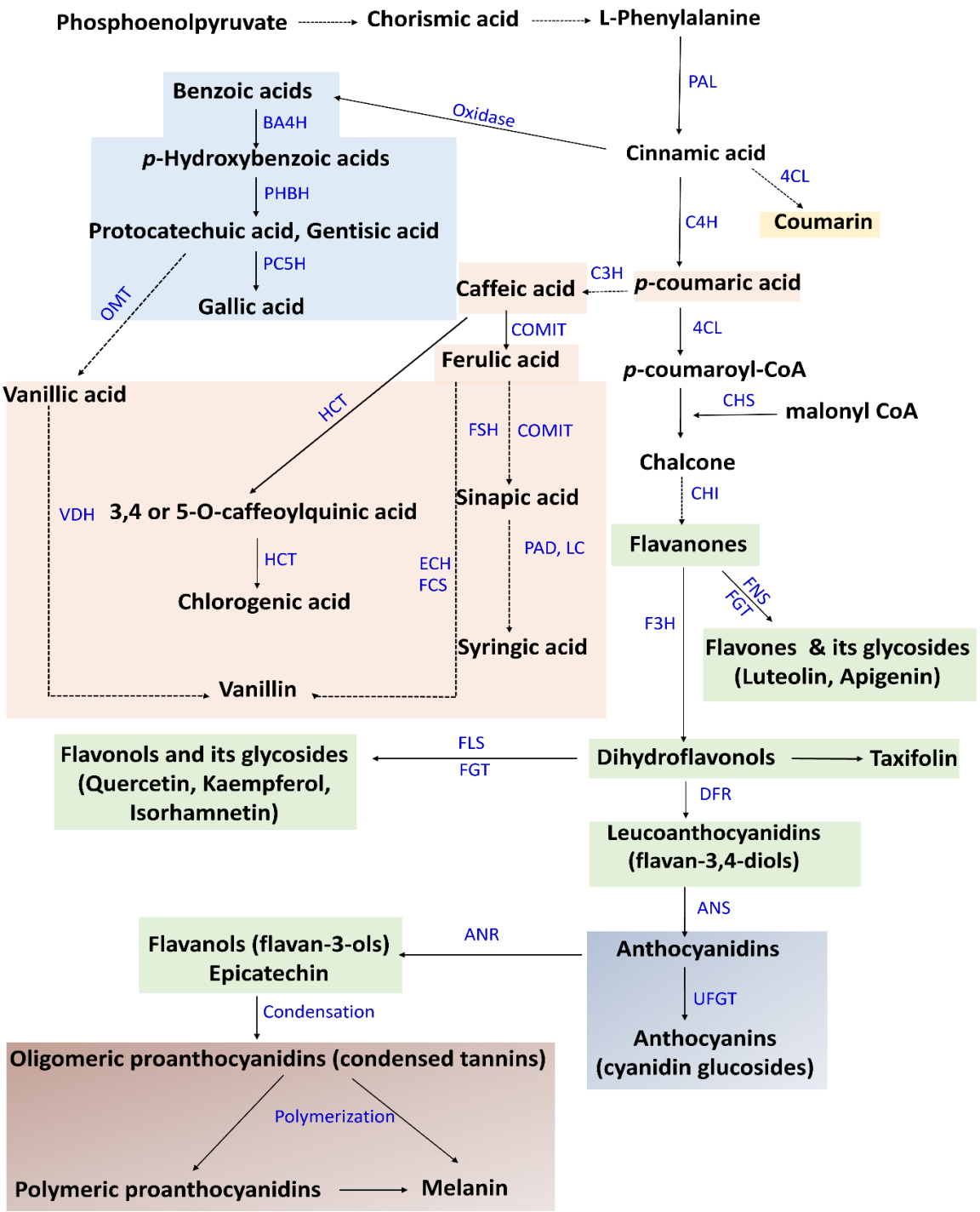

Figure 3: Biosynthesis pathway of phenolic compounds.

Abbreviations: PAL, phenylalanine ammonia-lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-coumaroyl CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; F3H, flavanone 3-hydroxylase; FNS, flavone synthase; FGT, flavonoid glycosyltransferase; FLS, flavanol synthase; DFR, dihydroflavonols reductase; ANS, anthocyanidin synthase; UFGT, flavonoid-3-O-glucosyltransferase; GT, glucosyltransferase; ANR, anthocyanidin reductase; BA4H, benzoic acid 4-hydroxylase; PC5H, protocatechuic acid 5 hydroxylase; HCT, hydroxycinnamoyl transferase; C3H, cytochrome; COMT, caffeoylshikimate esterase; ECH, enoyl-CoA hydratase/aldolase, FCS, trans-feruloyl-CoA; VDH Vanillin dehydrogenase; PAD, phenolic acid decarboxylase; LC, laccase.

1.4.2 Phenolic Compounds in Fruits

Fruits are rich sources of dietary phenolic compounds (Haminiuk et al., 2012). Epidemiological studies and meta-analyses have revealed that long-term polyphenol-rich diets protect against neurological disorders, diabetes, cancer, and osteoporosis (Rahman et al., 2022). Fruit bioactive substances, such as catechins, gallic acid, anthocyanins, ascorbic acid, and quercetin (Konstantinidi & Koutelidakis, 2019), help regulate weight, prevent obesity, and mitigate its metabolic effects. Nilsson et al. (2017) examined the effect of a 5-week intervention with a combination of berries on cognitive skills and cardiometabolic risk factors in healthy individuals. Polyphenols and dietary fiber can facilitate these benefits. Polyphenols and starch-digesting enzymes may unite to prevent postprandial hyperglycemia in individuals with type 2 diabetes through hydrophobic association and hydrogen bond formation between polyphenols and enzymes (Ali Asgar, 2013). Consumer needs and expectations have changed over time with a growing understanding of the nutritional qualities of fruits. Consequently, "functional foods," which contain phenolic compounds that can improve health, are gaining popularity (Milella et al., 2023).

Phenolic compounds can be categorized as soluble, hydrolyzable, and insoluble based on their chemical structure and localization within plant cells. Soluble phenolic compounds are present within the plant cell vacuole in soluble form (i.e., not physically and chemically bound to other molecules). However, hydrolyzable and insoluble phenolic compounds are covalently bound to structural components of the cell wall through an ester, ether, or carbon-carbon bond or entrapped into the food matrix macromolecules that have hydrophobic interactions (Acosta-Estrada et al., 2014; Shahidi & Yeo, 2016). Some fruits contain insoluble phenolic compounds that require alkaline treatment followed by acid precipitation for extraction. Previous studies have reported the presence of melanin in fruits such as watermelon seeds (Łopusiewicz, 2018), and persimmon (Qi et al., 2020). The strong bonding and complex food matrix present challenges in achieving efficient extraction and highlight the necessity to break these linkages. Therefore, efficient and selective analytical methodologies are required for the extraction of hydrolyzable and insoluble phenolic compounds. Because phenolic compounds bind to other cellular

components, such as lignin, cellulose, pectin, and hemicellulose, complete extraction may not be feasible using current methods.

Table 1: Extractability of phenolic compounds.

Phenolic compounds	**Extraction solvents**	**Extracted compounds**
Soluble	Organic solvents (methanol, ethanol, acetone, or their aqueous mixtures)	Aglycone and glucosides
Hydrolyzable	Hydrolysis with alkali (3 M) and extraction with ethyl acetate/diethyl ether	Esterified and glycosylated
Insoluble	Dissolution with alkali (2 M) and precipitation with acid at pH < 2	Lignin and melanin

1.4.3 Phenolic Compounds in Date Fruits

Dates are one of the most abundant fruits in the world, with hundreds of cultivars found in different regions. They are rich in soluble sugars (comprising 65–70% of the total weight), and the remaining weight is contributed by other constituents, such as dietary fiber (5–15%), phenolic compounds (up to 5%), protein, fat, ash, minerals, and vitamins on fresh weight basis (FW) (Alam et al., 2023). The composition variation depends on the cultivar type, ripening stage, and total moisture content. Date fruits are a rich source of various phenolic compounds, such as phenolic acids, which are caffeic, gallic, ferulic, *ρ*-coumaric, *ρ*-hydroxybenzoic, protocatechuic, syringic, and vanillic acids (Al-Farsi et al., 2005). In addition, they contain flavonoids, including flavones, flavonols, and flavanols, (Hammouda et al., 2013). Catechin monomers, proanthocyanidin oligomers, and polymers (i.e., condensed tannins) were reported in Deglet Noor, a Tunisian cultivar. They also noted that the degree of polymerization (DP) of proanthocyanidins at maturity ranges from 7-33, depending on the cultivar type (Hong et al., 2006). Dates are green in the initial stages of development (Hababouk and Kimri) when the fruit is metabolically active. In the Khalal (Bisr) stage, the fruits change color from green to yellow in most cultivars and amber or red in a few cultivars. Figure 4 shows the development of date fruits and their color changes. The color of different date fruits varies between yellow, brown, red, and

black owing to various combinations of pigments, including carotenoids, anthocyanins, tannins, and melanin (Gross et al., 1983).

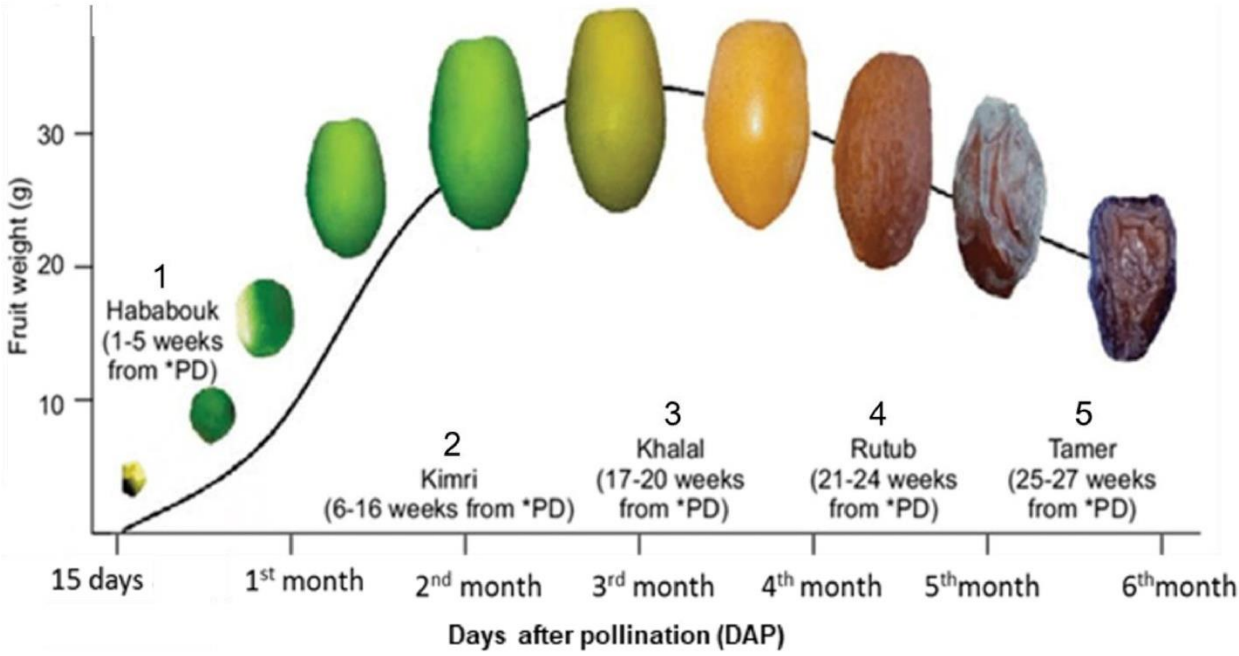

Figure 4: Date fruit developmental stages.

Modified from Al-Hajjaj and Ayad (2018) after permission from the Journal of Applied Horticulture.

A large portion of phenolic compounds are present in the tanniferous layer of date fruits (Figure 5). As mentioned previously, phenolic compounds have soluble, hydrolyzable, and insoluble forms. High-molecular-weight phenolic compounds, including lignin and melanin, are insoluble. Lignin is a complex aromatic polymer derived from precursors called lignols and is one of the main components of plant cell walls. The three monolignols—coniferyl, sinapyl, and *p*-coumaric alcohols—assemble in different proportions to form lignin polymers, which are guaiacol lignin (G-lignin), syringyl lignin (S-lignin), and *p*-hydroxyphenyl lignin (H-lignin) (Tobimatsu & Schuetz, 2019). The bioactivity of lignin depends on its molecular structure (Liu et al., 2018). Lignin is insoluble in most solvents and is difficult to purify (Zhang et al., 2020).

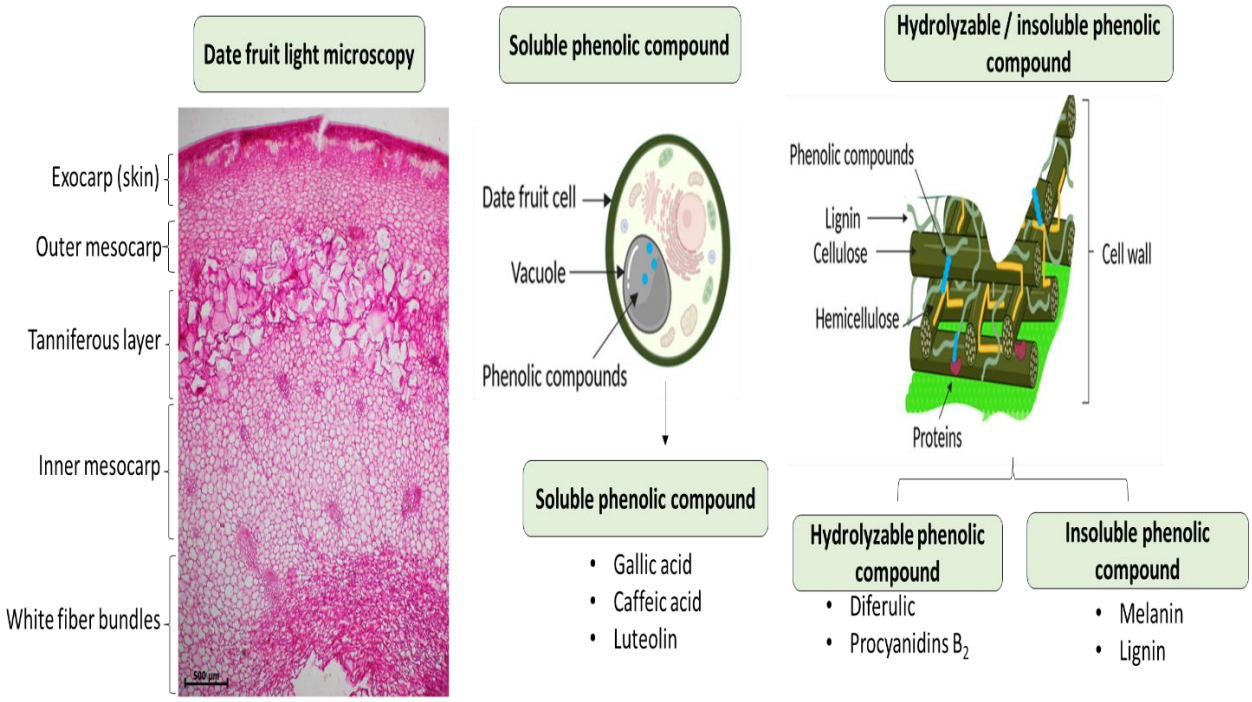

Figure 5: Localization of phenolic compounds in date fruits.

Light microscopy image of date fruit tissue stained with Mayer's hematoxylin reproduced from Kamal-Eldin et al. (2020).

Condensed tannins have been observed in date fruits (Hong et al., 2006), and melanin pigments may result from enzymatic browning in several cultivars (Al-Amrani et al., 2020). Condensation of catechins and low-molecular-weight proanthocyanidins into high-molecular-weight oligomers/polymers is associated with diminished bitterness and astringency after the green stage (Lea & Arnold, 1978; Riekstina-Dolge et al., 2014). A higher degree of oligomerization is associated with lower astringency, whereas tetramic and lower proanthocyanidin oligomers are related to strong bitterness (Brannan et al., 2001; Ma et al., 2014). The browning of dates and date products is associated with enzymatic and nonenzymatic reactions during fruit development and storage (Al-Amrani et al., 2020). Postharvest browning of dates primarily results from the oxidation of phenolic compounds by PPO and peroxidase (Daas Amiour & Hambaba, 2016). PPO can be involved in the *ortho*-hydroxylation of monophenols to diphenols, followed by oxidation to their quinones. Quinones polymerize into melanin and form brown pigments (Al-Amrani et al., 2020; Yoruk & Marshall, 2003).

1.4.4 Health Benefits of Date Fruits

Date fruits provide various health benefits (Ashraf & Hamidi-Esfahani, 2011; Idowu et al., 2020; Ibrahim et al., 2021). Several studies have reported the health benefits of date fruits based on evidence from *in vivo* studies conducted on laboratory animals, including rats, mice, and rabbits. Studies conducted on rats have shown anti-diabetic effects (Ibrahim et al., 2015; Saddi et al., 2018), antioxidant/tissue-protective effects (Pujari et al., 2011), and antihyperlipidemic properties (Ahmed et al., 2016). In rabbits, the antioxidant effect (Elkablawy et al., 2013), and neuroprotective effects were investigated in mice (Sheikh et al., 2016). The antitumor potential of date fruit extract was evaluated, and the expression of apoptotic genes was upregulated or downregulated to maintain proper cell functioning (Roshankhah et al., 2020). Date fruit extracts have a potential hypoglycemic effect and the ability to lessen cardiomyopathy in diabetic rats (Saddi et al., 2018). In addition, another study investigated the impact of Ajwa date fruit extract on liver cancer and noted that it may restore the regular activity of liver enzymes (Khan et al., 2017). Despite several health benefits of date fruit phenolic compounds, few epidemiological investigations have been conducted in human clinical trials.

Furthermore, Alkaabi et al. (2011) reported that date fruit consumption did not increase postprandial glucose levels in healthy diabetic individuals. Another study (Butler et al., 2022) investigated the safety of diabetic patient's consumption of date fruits. Bagherzadeh Karimi et al. (2020) published a systematic review of clinical trials examining the impact of different date fruit botanical parts on patients. According to their assessment of the literature reported from 2000 to 2019, robust clinical trials are necessary. Mirghani (2021) also conducted a systematic literature review of the effects of date fruits on glycemia among patients with diabetes from the first study published in 2020, according to which dates can lower plasma glucose levels despite their high sugar content. Further extensive long-term clinical trials are recommended to better understand the impact of dates on blood and insulin levels in patients with type 2 diabetes mellitus.

1.4.5 Analysis of Phenolic Compounds in Date Fruits

Several factors affect the extraction of phenolic compounds from fruits. The first factor is the sample preparation phase, which varies according to the fruit type and the

research goal. The second and most important factor is extraction parameters, such as solvent, time and temperature, agitation, material particle size, and solvent-to-solid ratio (Alara et al., 2021; Haminiuk et al., 2012; Khoddami et al., 2013; Pinelo et al., 2005). Aqueous mixtures of organic solvents, such as methanol, ethanol, and acetone, are mainly used to extract soluble phenolic compounds. Organic solvents (100%) have low solubility for polyphenols because of the strengthening of the hydrogen bonds between polyphenols and proteins. Increased solubility in aqueous organic solvents results from the weakening of hydrogen bonds in aqueous solutions (Rajbhar et al., 2015). Figure 6 shows an overview of the methods used for sample pretreatment, extraction, and analysis.

Table 2 provides an overview of studies conducted on the identification and quantification of date fruit phenolic compounds between 2005 and 2023. Most extraction methods use aqueous solutions of methanol or acetone as extraction solvents. LC-MS/MS and HPLC are frequently used methods for identification and quantification. Various phenolic compounds, including phenolic acids, flavonoids, and proanthocyanidins aglycone and their derivative forms, have been reported in date fruits at varying concentrations, depending on cultivar types, climatic conditions, extraction and analysis methods. However, earlier studies on date fruits have mainly examined soluble phenolic compounds that were extractable using organic solvents, such as acetone, methanol, or ethanol (Abu-Reidah et al., 2017; Al-Farsi et al., 2005; Khallouki et al., 2018; Najm et al., 2021). Al-Farsi et al. (2005) reported that alkaline and acid hydrolysis can extract hydrolyzable phenolic acids in the residue after the soluble fraction extraction. However, this analysis covers only phenolic acids, which does not cover other classes of phenolic compounds. Insufficient research on date fruit hydrolyzable phenolic content indicates the need for an in-depth investigation to unravel the hidden phenolic compound profile of date fruits. Table 3 provides an overview of studies conducted on date fruit antioxidant properties between 2005 and 2023.

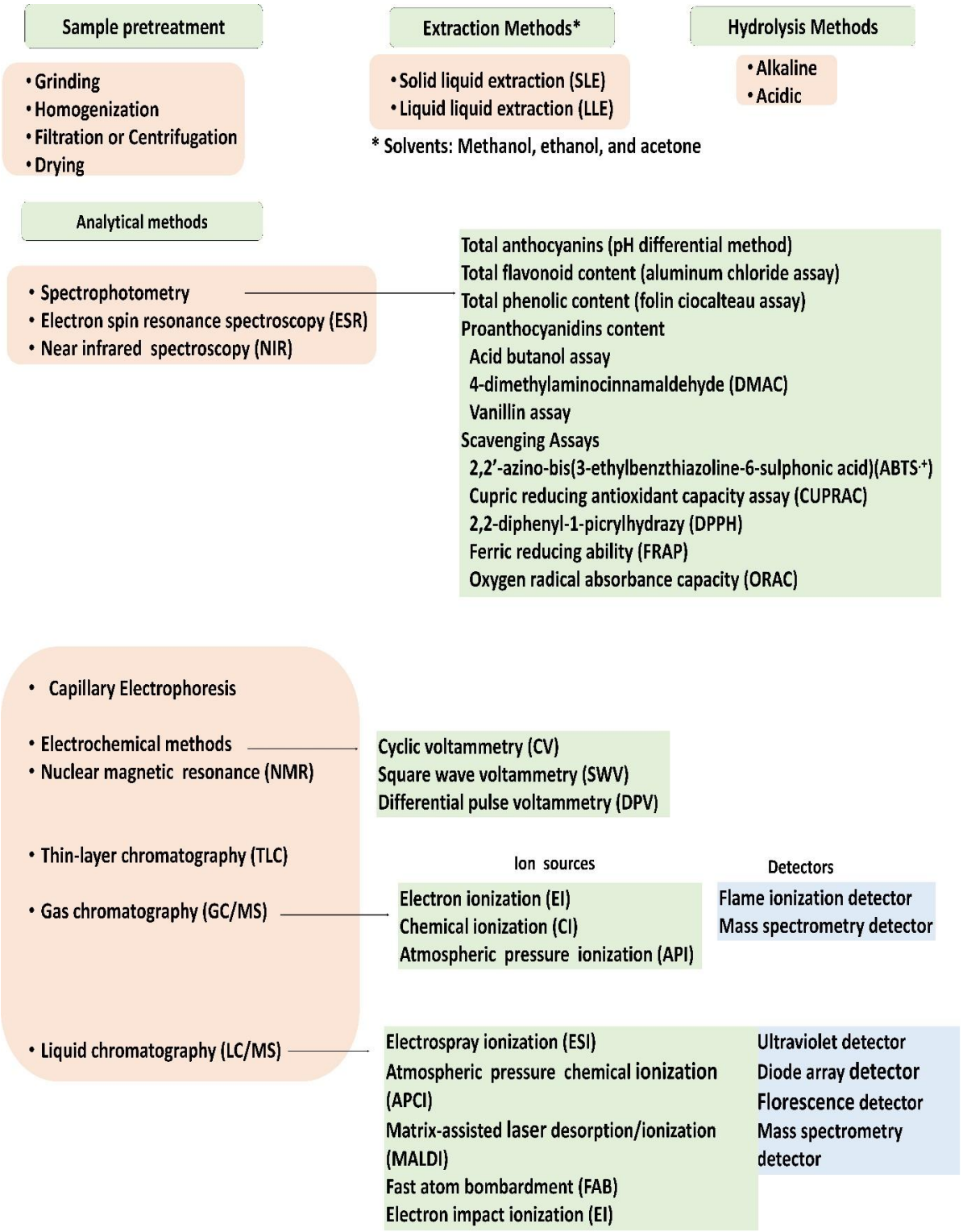

Figure 6: Extraction and analysis methods for phenolic compounds.

Table 2: Overview of studies conducted on date fruit identification and quantification from 2005 to 2023.

References	Extraction method	Analytical method	Compounds
Mansouri et al., 2005	Dates (100 g) were extracted using methanol (300 mL, 80% v/v)	LC-DAD-MS-ESI	Coumaric, ferulic, and sinapic acids and their derivatives, such as 5-o-caffeoyl shikimic acid
Al-Farsi et al., 2005	Dates (1 g) were extracted using 50% aqueous methanol or 70% aqueous acetone (40 mL) followed by alkaline hydrolysis (5 mL, 10 M NaOH) and acid hydrolysis (2.5 mL, 11 M HCl)	HPLC-DAD	Soluble phenolic acids (ferulic, protocatechuic, syringic, and vanillic acids) Hydrolyzable phenolic acids (caffeic, ferulic, gallic, *o*-coumaric, *p*-coumaric, *p*-hydroxybenzoic, protocatechuic, syringic, and vanillic acids)
Hong et al., 2006	Dates (10 g) were extracted using acetone:water:acetic acid (100 mL, 70:29.5:0.5 v/v/v)	HPLC-DAD/LC-MS-ESI	Flavonoid glycosides of apigenin, luteolin, and quercetin in isomeric forms, and flavonoid sulfates
Karasawa et al., 2011	Dates (1,000 g) were extracted using hot water (9,000 mL)	UPLC-DAD	Caffeic, chlorogenic, ferulic acid, and pelargonidin
Saleh et al., 2011	Dates (10 g) were extracted using water or methanol solution (90 mL, 99% v/v)	HPLC-DAD	Caffeic acid, catechin, and rutin
Kursinszki et al., 2011	Dates (5 g) were extracted in methanol (65 mL)	LC-MS-ESI	Flavonoid glycosides (luteolin and quercetin)
Hammouda et al., 2013	Date powder (10–60 mg) was extracted using methanol (1 mL, 99:1 v/v acetic acid)	LC-MS-ESI	Proanthocyanidin polymers (14 g/kg)
Benmeddour et al., 2013	Dates (2 g) were extracted using acetone (100 mL, 60% (v/v)	HPLC-DAD	Caffeic, ferulic, gallic acid, iso-quercitrin, luteolin, *p*-coumaric acid, rutin, and quercitrin
Farag et al., 2014	Date powder (150 mg) was extracted using methanol (6 mL)	UPLC/PDA/ESI–QTOF-MS	Flavones glycosides of apigenin, luteolin, and quercetin conjugates
Borochov-Neori et al., 2015	Dates (100 g) were extracted using acetone (300 mL, 99.5:0.5 v/v acetic acid)	HPLC-DAD	Caffeic, ferulic, and kaempferol derivatives
Kchaou et al., 2016	Dates (2 g) were extracted using acetone (20 mL, 70 % v/v)	HPLC-DAD	Caffeic acid, catechin, coumaric acid, ferulic acid, gallic acid, rutin, sinapic acid, syringic acid, trans-cinnamic acid, and vanillic acid
Abu-Reidah et al., 2017	Lyophilized dates (1 g) were extracted using methanol (5 mL, 75% v/v)	LC-UV-ESI-MS	Flavonoid glycosides of apigenin, chrysoeriol, isorhamnetin, 3-methyl-isorhamnetin, sulfates, malonyl derivative quercetin, luteolin, and kaempferol
Bouhlali et al., 2018	Dates (1 g) were extracted using acidified methanol (25 mL, 1 N HCl:methanol:water, 1:80:19 v/v)	HPLC-DAD	Caffeic acid, ferulic acid, gallic acid, *p*-coumaric acid, syringic acid, and rutin
Souli et al., 2018	Dates (1 g) were extracted using methanol (10 mL, 80% v/v)	LC-ESI-MS	Apigenin, caffeic acid, catechin, chlorogenic acid, epicatechin, ferulic acid, gallic acid, luteolin, *p*-coumaric acid, protocatechuic acid, quercetin, rutin, and syringic acid

Table 2: Overview of studies conducted on date fruit identification and quantification from 2005 to 2023 (Continued).

References	Extraction method	Analytical method	Compounds
Khallouki et al., 2018	Dates (25 g) were extracted using acetic acid (100 mL, 2% v/v)	HPLC-DAD LC-ESI-MS	Chelidonic acid, dicaffeoyl shikimic acid, ferulic acid, rutin, and taxifolin
Alahyane et al., 2019	Dates (2 g) were extracted using methanol (50 mL, 80% v/v)	HPLC-DAD	Caffeic acid, catechin, chlorogenic acid, ferulic acid, gallic acid, *o*-coumaric acid, rutin, and syringic acid
Abdul-Hamid et al., 2019	Dates (2 g) were extracted using ethanol (20 mL)	UHPLC-MS	Caffeic acid, kaempferol, proanthocyanidin, and quercetin derivates
Al Juhaimi et al., 2020	Date (3 g) was extracted using methanol (10 mL, 80% v/v)	HPLC-DAD	Apigenin 7 glucoside, benzene-1,2-diol syringic, caffeic acid, (+)-catechin, 3,4-dihydroxybenzoic acid, gallic acid, isorhamnetin, kaempferol, naringenin, *p*-coumaric acid, quercetin, trans-ferulic, resveratrol, rutin trihydrate, and trans-cinnamic acid
Siddiqi et al., 2020	Dates (10 g) were extracted using ethanol (100 mL)	HPLC-DAD	Caffeic acid, ferulic acid, gallic acid, *o*-coumaric acid, *ρ*-coumaric acid, syringic acid, and vanillic acid
Tassoult et al., 2021	Dates (5 g) were extracted using solvent mixtures (20 ml) and water, methanol:water (65:35 v/v) acetone:water (65:35 v/v)	HPLC-DAD	Caffeic acid, ferulic acid, gallic acid, luteolin, *o*-coumaric acid, *ρ*-coumaric acid, protocatechuic acid, quercetin, rutin, syringic acid, and vanillic acid
Najm et al., 2021	Dates (40 g) were extracted using solvent mixtures, 120 mL of water, 80% methanol, 70% acetone	UHPLC-ESI-QTOF-MS/MS	Derivatives of caffeic acid, ferulic acid, gallic acid, luteolin, quercetin, and sinapic acid
Khatib et al., 2022	Dates (12 g) were extracted using acetone (480 mL, 90% v/v)	HPLC-DAD-MS	Derivatives of cinnamic acid, chrysoeriol, kaempferol, luteolin, quercetin, and taxifolin
Bettaieb et al., 2023	Dates (20 g) were extracted using ethanol (60 mL, 80% v/v)	LC-ESI-MS	Apigenin, apigenin-7-o-glucoside, catechin (+), epicatechin, ferulic acid, gallic acid, kaempferol, luteolin, luteolin-7-o-glucoside, protocatechuic acid, *p*-coumaric acid, quercetin, quercetin-3-o-rhamnoside, and rutin
Muñoz-Bas et al., 2023	Dates (3 g) were extracted using acidified methanol (30 mL, 80% v/v).	LC-ESI-MS	Caffeic acid, catechin (+), (−)-epicatechin, hesperidin, isoquercitrin, rutin, and luteolin-7-o-glucoside

Abbreviations: DAD, diode array detector; ESI, electron spray ionization; GAE, gallic acid equivalent; HPLC, high-performance liquid chromatography; LC, liquid chromatography; MS, mass spectrometry; PDA, photodiode array detector; UHPLC, ultra-high-performance liquid chromatography; UPLC, ultra-performance liquid chromatography; QTOF, quadrupole time of flight

Table 3: Overview of studies conducted on antioxidant properties of date fruits from 2005 to 2023.

Reference	Extraction method	Analytical method	Results
Mansouri et al., 2005	Dates (100 g) were extracted using methanol (300 mL, 80% v/v)	DPPH, TPC	0.4–12.7 (µg sample/µg DPPH) 2.5–8.4 (mg GAE/100 g)
Al-Farsi et al., 2005	Dates (1 g) were extracted using 50% aqueous methanol or 70% aqueous acetone (40 mL) followed by alkaline hydrolysis (5 mL, 10 M NaOH) and acid hydrolysis (2.5 mL, 11 M HCl)	ORAC fluorescence, total anthocyanin, total carotenoids, TPC	8,212–20,604 (µmol TE/g) 0.24–1.52 (mg CYG/100 g) 0.92–3.03 (mg/100 g) 134–343 (mg FAE/100 g)
Biglari et al., 2008	Dates (100 g) were extracted using methanol (300 mL, 90% v/v)	ABTS, FRAP, TFC, TPC	23–500*(µmol TE/100 g) 12–387*(µmol Fe II/100 g) 1.6–82*(mg CE/100 g) 3–141*(mg GAE/100 g)
Saafi et al., 2009	Dates (200 mg) were extracted using methanol (2 mL, 50% v/v)	ABTS, DPPH, TPC	867–1,148 (µmol TE/100 g) 0.5–1.4 (EC_{50} µg/µg DPPH) 209–447 mg (GAE/100 g)
Nadeem & Anjum, 2011	Dates (1 g) were extracted using ethanol (10 ml, 80% v/v)	TPC	141–297 (mg GAE/100 g)
Saleh et al., 2011	Dates (10 g) were extracted using methanol (90 mL, 99% v/v)	DPPH, TPC	3–9.1 (mg/mL) 106–459 (mg GAE/100 g)
Singh et al., 2012	Dates (100 g) were extracted using methanol (300 mL, 90% v/v)	ABTS, DPPH, metal chelating assay, superoxide radical scavenging assay, TFC, TPC	84%–92% ABTS inhibition 70%–73% DPPH inhibition 80%–87% Chelating effect 29%–44% SRSA inhibition 25–34*(mg CEQ/100 g) 194–235*(mg GAE/100 g)
Amira et al., 2012	Dates (200 mg) were extracted using methanol (2 mL, 50% v/v)	ABTS, DPPH, reducing power, TFC, TCT, TPC	1–1.5 (mmol TE/100 g) 0.6–0.9 (AE µg sample/µg DPPH) 6–21 (mg sample/mL) 42–111 (mg CE/100 g) 40–110 (mg CE/100 g) 182–375 (mg GAE/100 g)
Zineb et al., 2012	Dates (5 g) were extracted using (50 ml) water, methanol (80% and 100%), and acetone (50% v/v)	DPPH, FRAP, TFC, TPC	0.09–2 (IC_{50} mg sample/mL) 3–7.5 (mM AEAC) 2–7*(mg QE/100 g) 85–164*(mg GAE/100 g)
Benmeddour et al., 2013	Lyophilized dates (2 g) were extracted using acetone (100 mL, 60% v/v)	DPPH, FRAP, ferrous ion chelating ability, hydrogen peroxide, TCT, TFC, TFOC, TPC	32%–8% DPPH scavenging capacity 336–1,175*(mg GAE/100 g) 49%–96% ferrous ion chelating capacity 15%–98% H_2O_2 scavenging capacity 83–525*(mg CE/100 g) 15–300*(mg QE/100 g) 7–37*(mg RE/100 g) 226–956*(mg GAE/100 g)
Salman Haider et al., 2013	Dates (0.5 g) were extracted using methanol (2 mL, 95% v/v)	TPC, DPPH	60–200*(mg GAE/100 g), 1.2–1.9 DPPH antiradical efficiency

Table 3: Overview of studies conducted on antioxidant properties of date fruits from 2005 to 2023 (Continued).

Reference	Extraction method	Analytical method	Results
Mohamed Lemine et al., 2014	Dates (10 g) were extracted using methanol (30 mL, 80% v/v)	DPPH, TFC, TPC	76–99*(µmol TE/100 g) 40–113*(mg QE/100 g) 406–661*(mg GAE/100 g)
Taouda et al., 2014	Dates (10 g) were extracted using methanol (100 mL, 80% v/v)	DPPH, TFC, TPC	0.007–0.033 (EC_{50} mg/ml) 0.010–0.38 (mg QE/100 g) 1.5–4.5 (mg GAE/100 g)
Farag et al., 2014	Date powder (150 mg) was extracted using methanol (6 mL)	TPC	233–1,897*(mg GAE/100 g)
Al-Jasass et al., 2015	Dates (2.5 g) were extracted using methanol (20 mL, 80% v/v)	ABTS, DPPH, FRAP, OARC, TPC	341–1,300*(µmol TE/100 g) 3.2–3.5*(µmol TE/100 g) 3.3–5.2*(µmol TE/100 g) 189–243*(µmol TE/100 g) 33–125*(mg GAE/100 g)
Borochov-Neori et al., 2015	Dates (100 g) were extracted using acetone (300 mL, containing 0.5% acetic acid v/v)	DPPH, FRAP	8–22 (%OD DPPH free radical scavenging capacity) 0.81–0.88 (VCE/GAE, mole ratio)
Ali Haimoud et al., 2016	Dates (100 g) were extracted using methanol (300 mL, 80% v/v)	*β*-Carotene-linoleic acid system, DPPH, FRAP, total antioxidant using phosphomolybdenum assay, TFC, TFOC, TPC	50–77 (%inhibition by *β*-carotene-linoleate model system), 206–380 (IC_{50} µg/mL) 0.4–1.4*(mg REQ/100 g) 43–90 (µmol of ascorbic acid/g of extract) 19–56*(µmol Fe (II)/100 g) 1–4.2*(mg CEQ/100 g) 2.1–6.5*(mg GAE/100 g)
Mohammad et al., 2015	Dates (1 g) were extracted using methanol (10 mL, 80% v/v)	FRAP, TPC	0.4–1.1 (mMol Fe II/100 g) 38–104 (mg GAE/100 g)
Mohamed et al., 2016	Dates (2 g) were extracted using methanol (20 mL, 80% v/v)	ABTS, DPPH, TFC, TPC	0.5–4.4 (IC_{50} mg GAE) 1.6–8.2 (IC_{50} mg GAE) 27–191*(mg CE/100 g) 122–247*(mg GAE/100 g)
Bouhlali et al., 2017	Dates (30 g) were extracted using methanol (150 mL, 90% v/v)	ABTS, DPPH, FRAP, TCT, TFC, TPC	384–847*(µmol TE/100 g) 2,050–6,250 (IC_{50} g/L) 407–861*(µmol TE/100 g) 57–92*(mg CE/100 g) 69–208*(mg RE/100 g) 332–537*(mg GAE/100 g)
Souli et al., 2018	Dates (1 g) were extracted using methanol (10 mL, 80% v/v)	ABTS, DPPH, FRAP, TCT, TFC, TFOC, TPC	865–1,617 (µmol TE/100 g) 0.16–0.31 (IC_{50} mg/mL) 625–1,229 (µmol TE/100 g) 37–41.8 (mg CE/100 g) 38.1–58 (mg CE/100 g) 9.7–23.4 (mg RE/100 g) 99–124 (mg GAE/100 g)
Verde et al., 2019	Dates (100 g) were extracted using methanol (300 mL, 90% v/v)	DPPH, TFC, TPC	13–33 (mMol TE/100 g) 18–49 (mg CE/100 g) 105–240 (mg GAE/100 g)
Alahyane et al., 2019	Dates (2 g) were extracted using methanol (50 mL, 80% v/v)	DPPH, FRAP, TCT, TFC, TPC	2–10 (IC_{50} mg/mL) 0.2–2 (IC_{50} mg/mL) 2–216*(mg QE/100 g) 5–152*(mg CE/100 g) 101–4,679*(mg GAE/100 g)

Table 3: Overview of studies conducted on antioxidant properties of date fruits from 2005 to 2023 (Continued).

Reference	Extraction method	Analytical method	Results
Abdul-Hamid et al., 2019	Dates (2 g) were extracted using ethanol (20 mL)	DPPH, TPC	27–93 (%DPPH scavenging capacity) 3–10∗(mg GAE/g)
Siddiqi et al., 2020	Dates (10 g) were extracted using ethanol (100 mL)	TPC	104–164 (mg GAE/100 g)
Tassoult et al., 2021	Dates (5 g) were extracted using solvent mixtures (20 mL): water, methanol:water (65:35 v/v), and acetone:water (65:35 v/v)	ABTS, DPPH, FRAP, TPC,	79–142∗(mMoL TE/kg) 6–15 (IC50 mg/mL) 70–130∗(mMoL TE/kg) 95–193∗(mg GAE/100 g)
Bensaci et al., 2021	Dates (5 g) were extracted using methanol (50 mL, 80% v/v)	DPPH, FRAP, TFC, TPC	0.07–0.18 (IC50 mg/mL) 5–9 (mMoL AEAC) 3–12∗(mg QE/100 g) 154–279∗(mg GAE/100 g)
Djaoudene et al., 2021	Dates (1 g) were extracted using ethanol (20 mL, 50% v/v)	ABTS, DPPH, TFC, TPC,	2–4 (mg TE/g) 1.2–2.4 (mg TE/g) 0.2–0.5 (mg QE/g) 3–5 (mg GAE/g)
Bettaieb et al., 2023	Dates (20 g) were extracted using ethanol (60 mL, 80% v/v)	ABTS, DPPH, TCT, TFC, TPC	28–107 (mg TE/100 g) 21–132 (mg TE/100 g) 40–147 (mg CE/100 g) 45–117 (mg RE/100 g) 10–297 (mg GAE/100 g)
Hamdi et al., 2023	Dates (100 g) were extracted using methanol (300 mL, 80% v/v)	ABTS, DPPH, FRAP, TPC	69–208 (µg TE/mL) 2,717–3,060 (µg TE/mL) 220–239 (µg TE/mL) 217–570 (mg GAE/100 g)
Bahiani et al., 2023	Dates (2 g) were extracted using a mixture of methanol, acetone, and water (40 mL, 7:7:6 v/v)	ABTS, DPPH, FRAP, TCT, TFC, TPC	865–1,815∗(µmol TE/100 g) 0.02–0.176 (IC50 mg/L) 863–1,980∗(µmol TE/100 g) 21–76∗(mg CE/100 g) 14–59∗(mg CE/100 g) 97–372∗(mg GAE/100 g)
Jdaini et al., 2023	Dates powder (0.6 g) was extracted using water and acetone (6 mL, 50 %v/v)	DPPH, FRAP, TFC, TPC	3.4–5.1∗(IC50 g/L) 855–1,662∗(µmol TE/100 g) 87–190∗(mg QE/100 g) 209–496∗(mg GAE/100 g)
Muñoz-Bas et al., 2023	Dates (3 g) were extracted using acidified methanol (30 mL, 80% v/v)	ABTS, DPPH, FIC FRAP	0.9–1.1∗(mg TE/g) 26–32∗(µg TE/g) 3.7–4.6∗ (µg TE/g) 0.6–0.7∗(µg TE/g)

(*) Dry weight Basis. Abbreviations: AE, antiradical efficiency; AAE, ascorbic acid equivalent; ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; CE, (+)-catechin equivalent; CTC, condensed tannin content; CYG, cyanidin 3-glucoside equivalents; DPPH, 2-diphenyl-1-picrylhydrazyl; FAE, ferulic acid equivalent; FRAP, ferric reducing antioxidant power; FIC, ferrous ion chelating activity; GAE, gallic acid equivalent; OD, optical density; ORAC, oxygen radical absorbance capacity; QE, quercetin equivalent; RE, rutin equivalent; SRSA, superoxide radical scavenging ability; TCT, total condensed tannins; TFC, total flavonoid content; TFOC, total flavonols content; TPC, total phenolic content; TE, Trolox equivalent; VCE, vitamin C equivalents

Chapter 2: Methodology

2.1 Sample Collection

Samples used in the studies included in this thesis are shown in Table 4. Fruit samples were collected at the Tamar stage (full maturity) from three different batches per cultivar, but the origin of the different samples is not known. The samples were either frozen or stored at 4°C until analysis within 2 weeks.

Table 4: The cultivars used in this thesis and their origins.

Origin	Cultivars*	Collected from
UAE	Anwan, Barhi, Boumaan, Dabbas, Fard, Khalas, Khedrawi, Khasab, khenaizi, Lulu, Medjool, Neghal, Naptit saif, Reziz, Saqei, Shishi, and Zahidi (Studies I, II, III, and IV)	Al Foah Dates Factory (Al Saad, Abu Dhabi, UAE)
Pakistan	Aseel, Rabbi, Zahidi, Muzafati, Kurmoon, Karblain, Kupro, Basra, Jan swore, Begum Jangi, and Dhakki (Study II)	Central dates market (Karachi, Pakistan)
Tunisia	Deglet Nour (Study II)	Al Madina factory (Tunis, Tunisia)
Saudi Arabia	Ajwa and Safawi (Studies I, III, and IV)	Market (Al Ain, Abu Dhabi, UAE)

2.2 Analytical Methods

An overview of the analytical methods used across all objectives is shown in Figure 7 (refer to Papers I–IV for detailed methods). Total antioxidants assays were performed on soluble phenolic compounds using 80% methanol, and hydrolyzable phenolic compounds were extracted from the residue using ethyl acetate after alkaline hydrolysis (NaOH, 2M). In addition, UPLC-QTOF-MS and UPLC-DAD were utilized to investigate the identification and quantification of phenolic compounds in date fruits. Total antioxidant activity was assessed using methods such as TPC analysis (Singleton & Rossi, 1965) and radical scavenging assays, including ABTS (Rice-Evans & Miller, 1995), FRAP (Benzie & Strain, 1996), and DPPH (Blois, 1958). These assays cause color formation or discoloration upon reaction, which is measured using a spectrophotometer.

The insoluble phenolic content that was not extractable in organic solvents with or without alkaline hydrolysis was examined for the characteristic features of melanin using several physiochemical characterization techniques, electron paramagnetic resonance (EPR), and nuclear magnetic resonance (NMR) with assistance from computational modeling that employed density functional theory (DFT). Melanin extracted from date fruits was tested for antioxidant and antimicrobial activities.

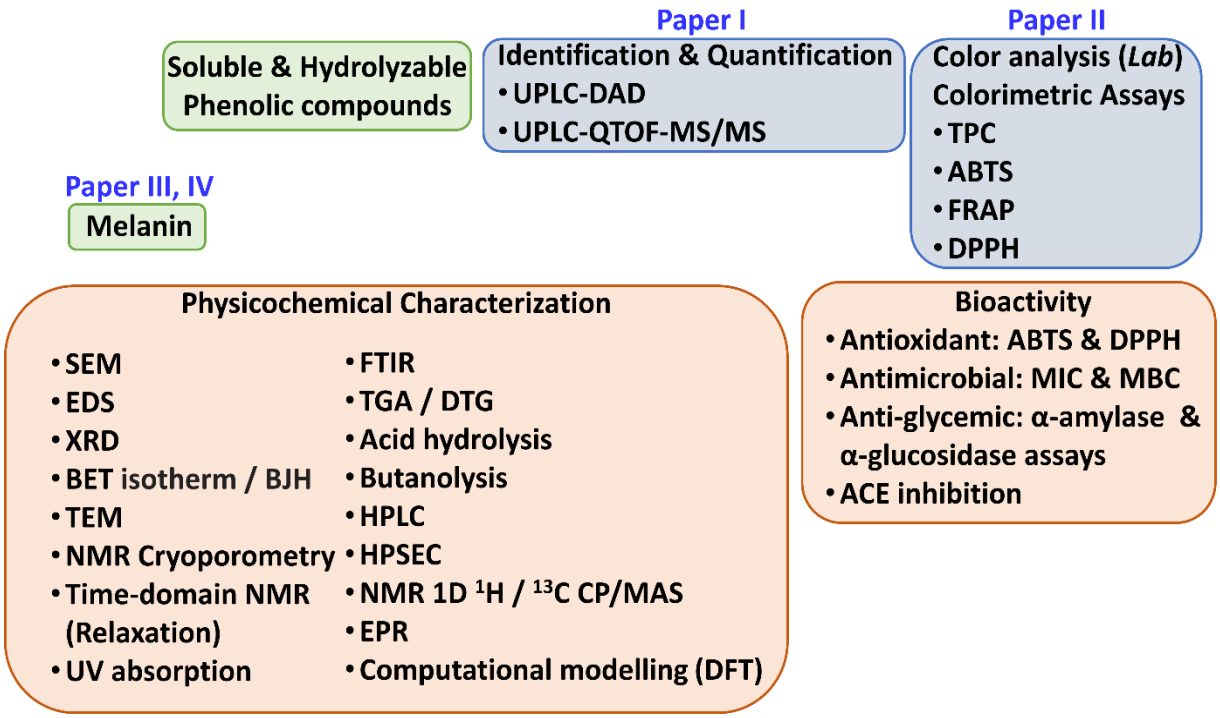

Figure 7: Analytical methods followed in Papers I–IV.

2.3 Statistical Analysis

The analysis was based on three biological replicates each analyzed in triplicate (n = 3*3). Principal component analysis and Pearson's correlation were used in Paper II and partial least regression analysis (variable importance projection) was used in Unpublished data.

Chapter 3: Results and Discussion

3.1 Phenolic Composition of Date Fruits (Paper I)

This study identified and quantified soluble and hydrolyzable phenolic compounds in date fruits. The extraction of soluble and hydrolyzable phenolic compounds from 18 cultivars was followed by their identification using LC-MS/MS and quantification using UPLC-DAD. This study is the first on the LC-MS/MS identification of hydrolyzable phenolic compounds in date fruits. Molecular ions and fragmentation patterns assisted in identifying 45 peaks; however, 14 remained unidentified (Table 1, Paper I). The concentration of individual phenolic compounds estimated from UPLC-DAD indicates that date cultivars have low variability in phenolic content (Figure 8). This study can be considered as the first screening study and further studies with a much larger number of samples are needed for proper comparison and deeper understanding of phenolic compounds profiles and their influencing factors. Soluble and hydrolyzable phenolic compounds were present in equal portions, indicating that hydrolyzable phenolic compounds are essential in these fruits. The phenolic compounds proanthocyanidins B_1 and B_2 were present in the hydrolyzable extracts. However, no distinct peaks were identified in any date fruit cultivars for trimers or greater proanthocyanidin oligomers in this study. The literature has revealed a hump possibly caused by the high molecular weight of proanthocyanidins in reversed-phase chromatography (Sirisena et al., 2017). Reversed-phase chromatography can only separate up to the degree of polymerization (DP-4) (Symma & Hensel, 2022). Notably, high-molecular-weight proanthocyanidins have been previously reported in date fruits (Hammouda et al., 2013; Hong et al., 2006). The use of degradation methods for proanthocyanidins, such as thiolysis and phloroglucinolysis before chromatographic separation, helps identify and quantify high-molecular-weight proanthocyanidins. The degree of polymerization of proanthocyanidins (7-33 DP) was reported by Hammouda et al. (2013) after phloroglucinolysis. proanthocyanidins polymers (DP > 10) were investigated by Hong et al. (2006) using normal phase chromatography in date fruits. In mass spectrometry (MS), high abundance of low- molecular-weight causes ion suppression of high-molecular-weight compounds (De Marchi et al., 2014).

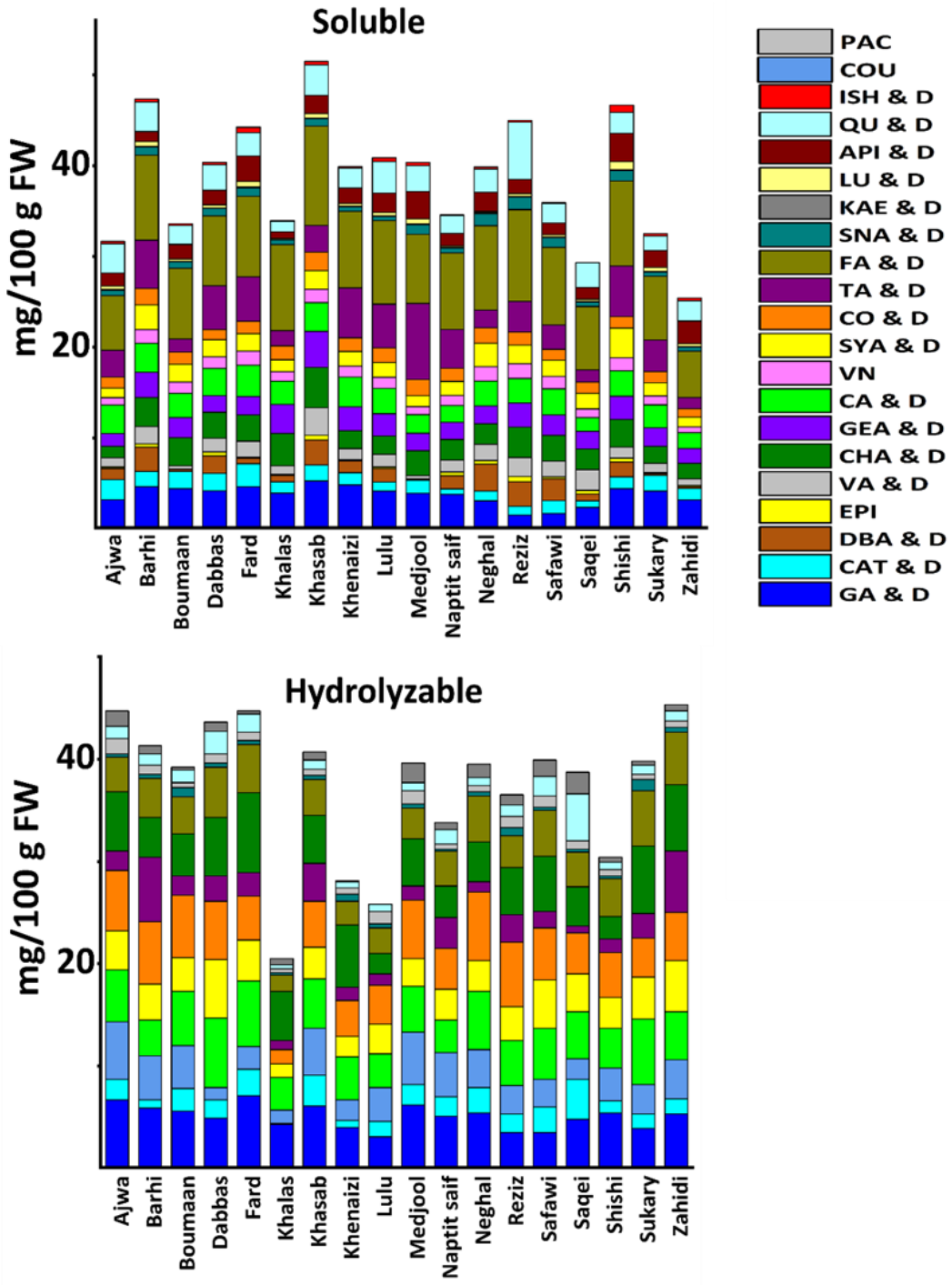

Figure 8: The concentration of soluble and hydrolyzable phenolics using UPLC-DAD at 280 nm (Paper I).

Abbreviations: GA & D, gallic acid and derivatives; CAT & D, protocatechuic acid and derivatives; VA & D, vanillic acid and derivatives; SYA & D, syringic acid and derivatives; DBA & D, 3,5-dihydroxybenzoic acid and derivatives; CA & D, caffeic acid and derivatives; VN, vanillin; CO & D, *p*-coumaric acid and derivatives; SNA & D, sinapic acid and derivatives; GEA & D, gentisic acid and derivatives; FA & D, ferulic acid and derivatives; LU & D, luteolin and derivatives; API & D; apigenin and derivatives; KAE & D, kaempferol and derivatives; QU & D, quercetin and derivatives; ISH & D, isorhamnetin and derivatives; CHA & D, chlorogenic acid and derivatives; TA & D, taxifolin and derivatives; EPI, epicatechin; PAC, proanthocyanidins B_2.

3.2 Total Antioxidant Activity of Date Fruit Extracts (Papers I and II)

The antioxidant activity of soluble and hydrolyzable phenolic compounds is shown in Figure 9 using the Folin–Ciocalteu $ABTS^{\cdot+}$, FRAP, and DPPH methods (Paper II). Most cultivars had a higher TPC in their soluble extracts than in their hydrolyzable extracts. Only a few cultivars exhibited greater antioxidant activity in the hydrolyzable fraction than in the soluble fraction in the $ABTS^{\cdot+}$ assay. Conversely, the hydrolyzable fractions in the FRAP assay demonstrated increased activity. The DPPH assay revealed a heterogeneous pattern in the soluble and hydrolyzable fractions, with certain cultivars exhibiting greater activity in the soluble fraction and others in the hydrolyzable fraction. In addition, the correlation between TPC, antioxidant assays, and color parameters (Lab) was investigated to identify significant correlations. Person correlation analysis (Table 5) demonstrated that most antioxidant assay data and color parameters did not exhibit any significant correlation. Only a few assays showed a weak correlation, such as ABTS *versus* FRAP (hydrolyzable extract) and FRAP *versus* DPPH (soluble extract).

According to the partial least regression analysis of UPLC data for phenolic compounds total (soluble + hydrolyzable extracts), only nine phenolic compound aglycones were found significant using VIP projections for TPC and antioxidant assays (Figure 10) (unpublished data). The presence of conjugated phenolic compounds, in which sugars obstruct the active –OH antioxidant groups, may explain why some phenolic compounds do not significantly contribute to antioxidant assays. Another explanation may be the structure–activity relationship between antioxidant tests and phenolic compounds. No evidence has been provided to support the robustness, dependability, or effectiveness of these analytical techniques with dates or other fruits and vegetables. For example, reducing sugars and ascorbic acid are matrix constituents that can impede the tests. These results revealed that these assays cannot investigate the antioxidation potential, mainly for complex matrices of phenolic compounds, such as those in date fruits. The use of different units, calibration standards, curves, and extraction methods make comparison of antioxidant assay results difficult (Schaich et al., 2015; Zeb, 2021).

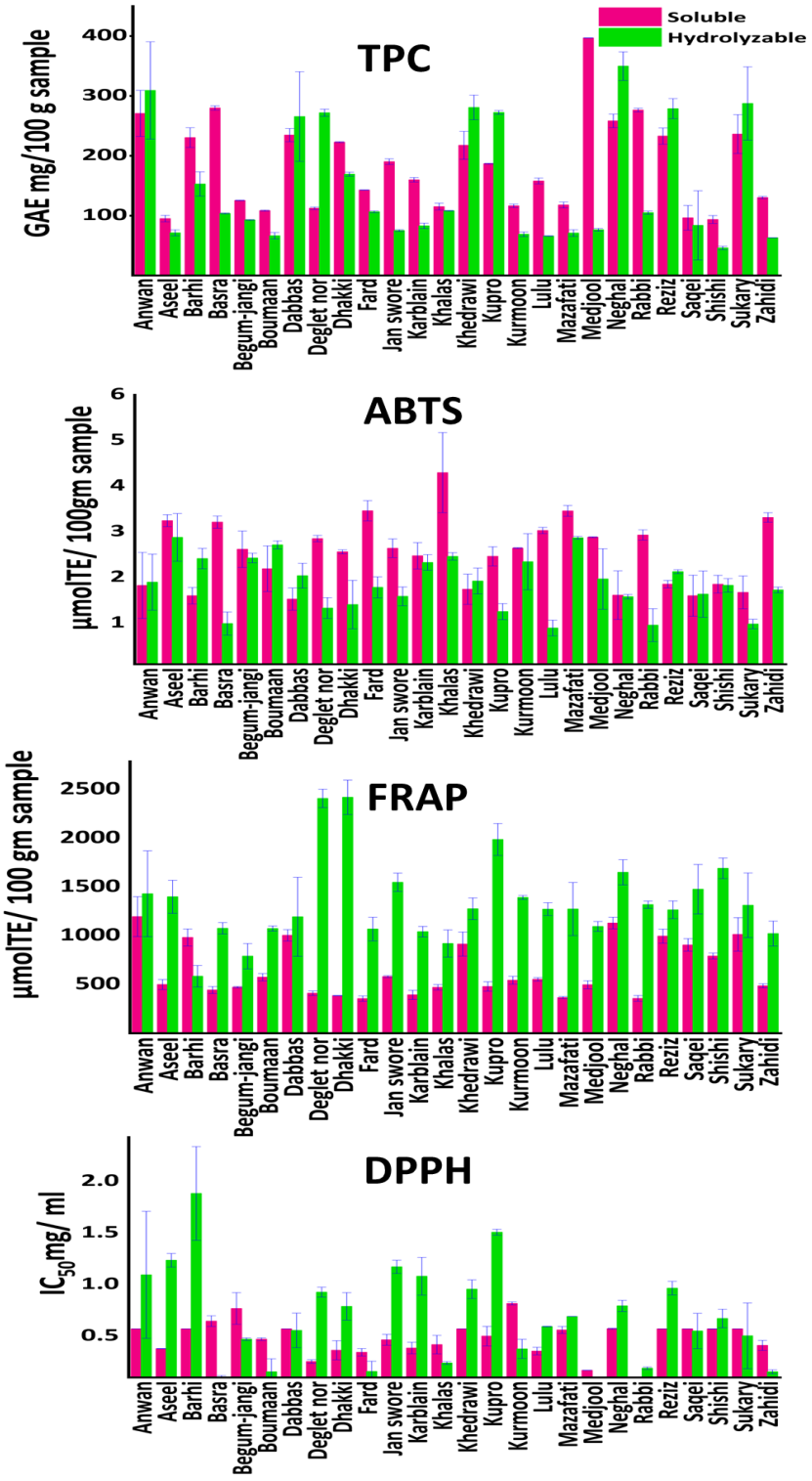

Figure 9: Total phenolic content and antioxidant assays in soluble and hydrolyzable extracts of date fruits (Paper II).

Abbreviations: ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; DPPH, diphenyl-1-picrylhydrazyl; FRAP, ferric reducing antioxidant power; GAE, gallic acid equivalent, TPC, total phenolic content; TE, Trolox equivalent.

Table 5: Pearson's correlation coefficients between the different antioxidant activity assay methods and color parameters (Paper II).

Parameter	T-S	T-HYD	A-S	A-HYD	F-S	F-HYD	D-S	D-HYD	L*	a*
T-HYD	**0.402***									
A-S	−0.252	**−0.538****								
A-HYD	−0.375	−0.278	0.097							
F-S	0.288	**0.632****	**−0.816****	−0.022						
F-HYD	−0.073	0.349	−0.113	**−0.418***	−0.078					
D-S	−0.228	0.150	**−0.391***	0.276	**0.442***	−0.202				
D-HYD	−0.042	0.374	**−0.403***	0.140	0.332	0.224	0.157			
L*	−0.370	−0.286	0.235	0.168	−0.178	−0.073	0.124	−0.047		
a*	−0.255	−0.132	0.143	−0.021	−0.303	0.178	−0.025	0.126	**0.652****	
b*	−0.158	−0.179	0.221	−0.125	−0.247	−0.050	0.053	−0.149	**0.785****	**0.724****

Abbreviations: T-S, total phenolic content (soluble); T-HYD, total phenolic content (hydrolyzable); F-S, FRAP (soluble); F-HYD, FRAP (hydrolyzable); A-S, $ABTS^{\cdot+}$ (soluble); A-HYD, $ABTS^{\cdot+}$ (hydrolyzable); D-S, DPPH (soluble); D-HYD, DPPH (hydrolyzable); L*, lightness; a*, red color; b*, yellow color. Correlations are significant (two-tailed) at the 0.05 level* and 0.01 level**.

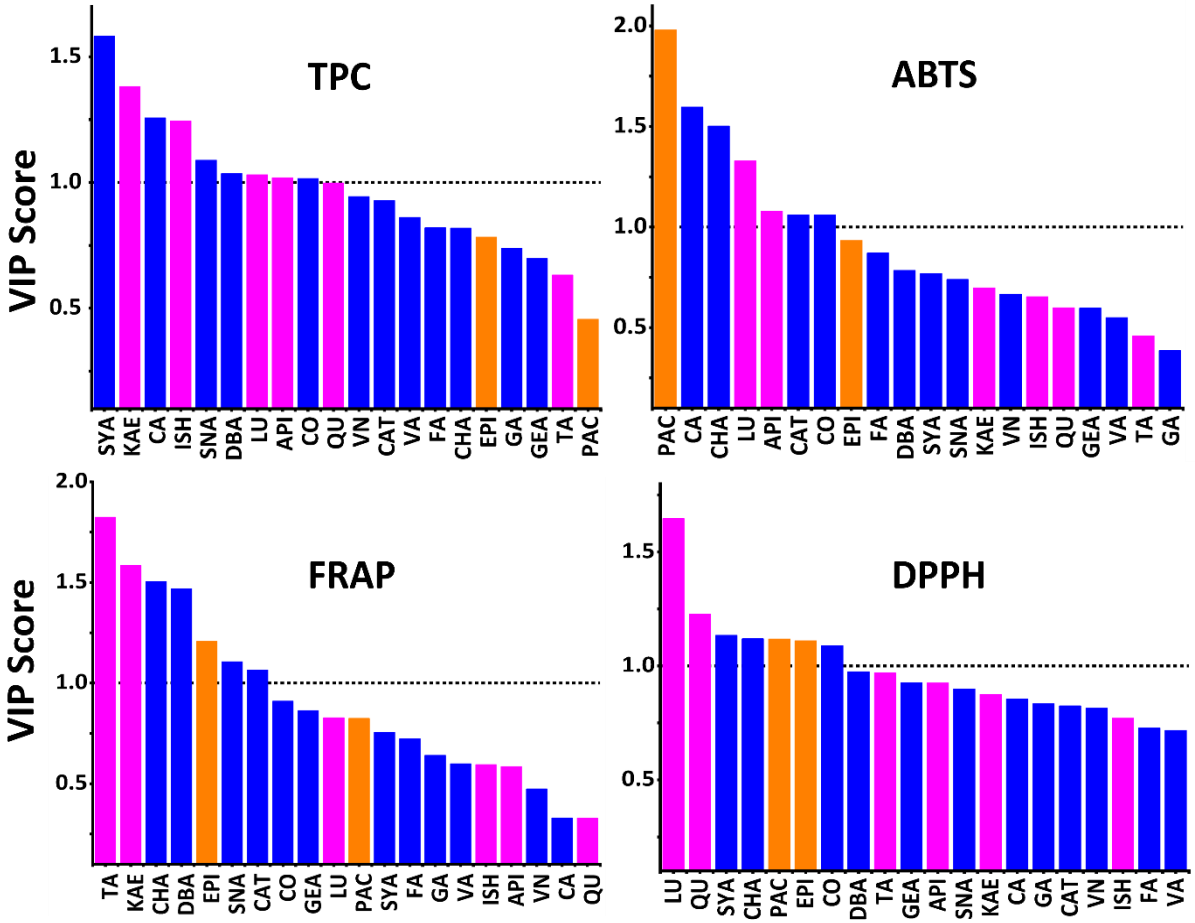

Figure 10: The VIP projection of variables (phenolic compounds) in antioxidant assays using PLS regression (unpublished).

Abbreviations: ABTS, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; API, apigenin; CA, caffeic acid; CHA, chlorogenic acid; DBA, 3,5-dihydroxybenzoic acid; DPPH, diphenyl-1-picrylhydrazyl; EPI, epicatechin; FRAP, ferric reducing antioxidant power; FA, ferulic acid; GA, gallic acid; GEA, gentisic acid; ISH, isorhamnetin; KAE, kaempferol; LU, luteolin; CO, *p*-coumaric acid; PAC, proanthocyanidins B_2; CAT, protocatechuic acid; QU, quercetin; SNA, sinapic acid; SYA, syringic acid; TPC, total phenolic content; TA, taxifolin; VA, vanillic acid; VN, vanillin.

3.3 Extraction and Characterization of Date Fruit Melanin (Papers III and IV)

This study is to extract and characterize melanin from date fruits. Date fruits contained high levels of insoluble allomelanin (1.2–5.1%) (Figure 11). Several methods were followed to assign the extracted material as melanin, including insolubility in organic solvents, solubility in alkaline solutions, precipitation at acidic pH, featureless UV absorption spectrum, and amorphous graphene-like granular structure. Date fruit melanin is an example of a thermostable polymeric compound composed of carbon (64.6%) and

oxygen (30.6%); however, no nitrogen or sulfur was found in the energy-dispersive X-ray spectroscopy analysis (Paper III).

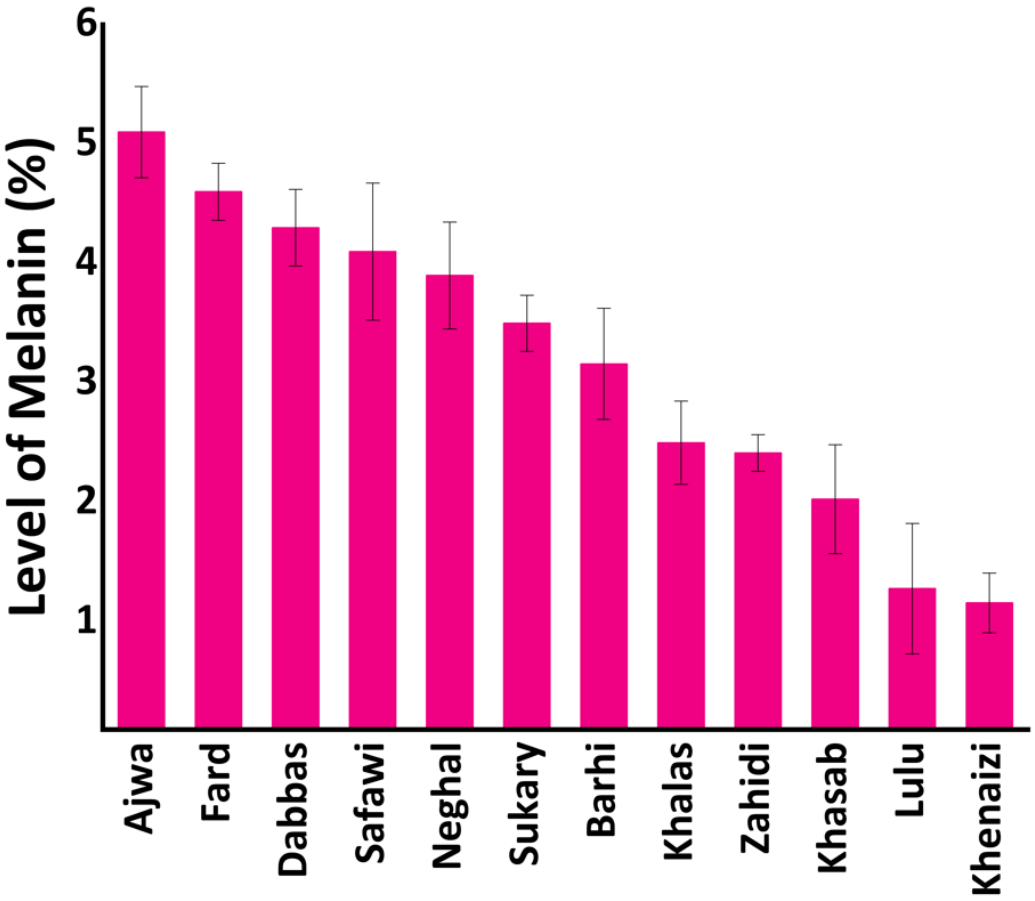

Figure 11: Levels (%) of melanin in twelve date fruit cultivars (Paper III).

Light microscopy (Figure 12) revealed that melanin was localized in the tanniferous layer after staining with *p*-dimethylaminocinnamaldehyde (DMACA). In addition, transmission electron microscopy showed that the melanin particles are aggregates. This aggregation phenomenon may depend on the method of extraction and acid precipitation step that leads to agglomerated particles of irregular shapes and dimensional variability from 43 to 350 µm. The porosity of the melanin granules varied from 10 to 1,000 Å by NMR cryoporometry. Date fruit melanin exhibited significant bioactive properties, such as antimicrobial activity, alpha-amylase, alpha-glucosidase, and ACE inhibition.

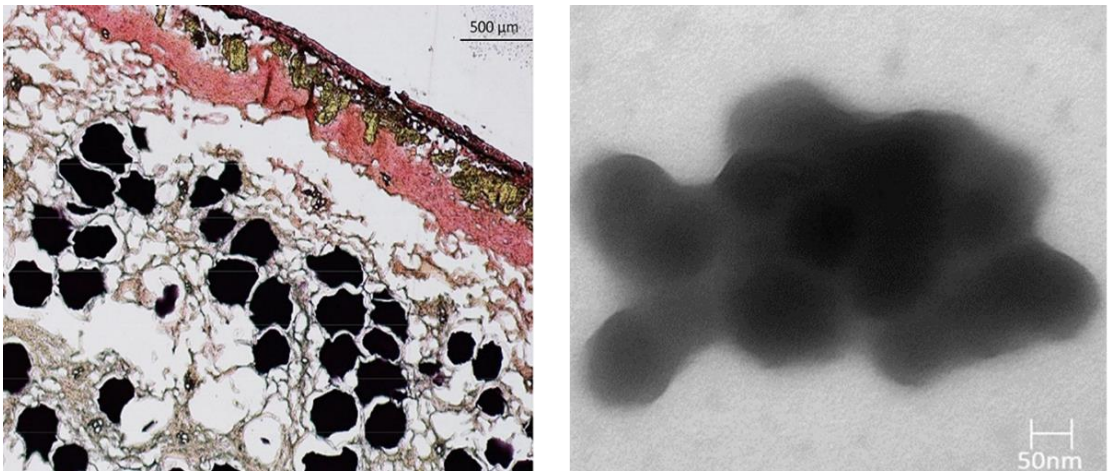

Figure 12: Localization of melanin in the tanniferous layer of date fruits using light microscopy stain with DMACA at 500 µm and transmission electron micrograph of melanin at 50 nm (Papers III and I).

However, the extracted melanin may include other alkali-soluble compounds, such as hemicellulose and lignin, precipitating at a pH of 2. Melanin analysis before and after acid treatment showed no significant differences in its characteristics, indicating that the portion of lignin and hemicellulose might not be adequately hydrolyzed by acid treatment. The paramagnetic properties of date fruit melanin were investigated using EPR, and the spectra are shown in Figure 13. Strong resonance absorption was observed in the date fruit melanin EPR spectra, comprising symmetrical single lines without hyperfine splitting. Differences in paramagnetic radical concentrations between cultivars caused variations in the measured signal intensity. Proper comprehension of the EPR behavior of date fruit melanin will not be possible unless the chemical structure of this melanin is fully understood.

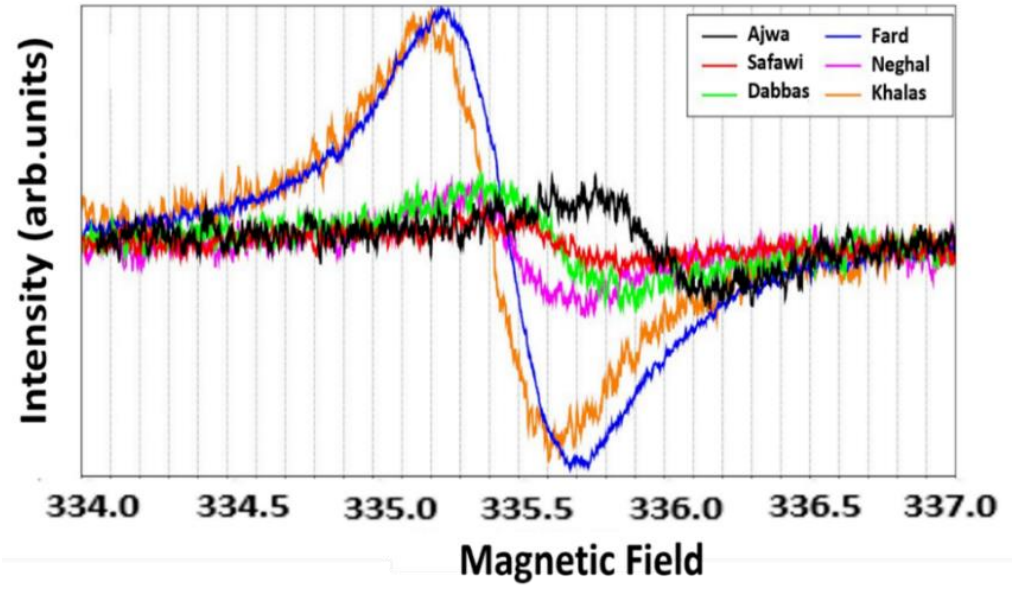

Figure 13: Electron paramagnetic resonance (EPR) spectrum of melanin extracted from six cultivars (Paper IV).

Figure 14 represents the theoretical ^{1}H-NMR and ^{13}C-NMR for (-)-epicatechin monomer and pentamer. The aromatic signals in theoretical chemical shifts have a slight deviation as compared to experimental chemical shifts supporting a proanthocyanidins-based stacked structure. This indication was further confirmed by EPR simulation studies using (-)-epicatechin radical through DFT, which showed that melanin has oligomeric structures of (-)-epicatechin with four or more molecular units (Figure 15). It was difficult to determine the precise size of the oligomer(s) because the g-factor of EPR stabilized after 4–5 oligomeric units. The molecular weight estimated using high-performance size exclusion chromatography revealed that the molecular weight of melanin ranged from 569 to 3,236 kDa, indicating that melanin in date fruits is based on (-)-epicatechin oligomers (2–11 units). However, further structural clarification *via* MALDI-TOF analysis is required to fully realize this potential.

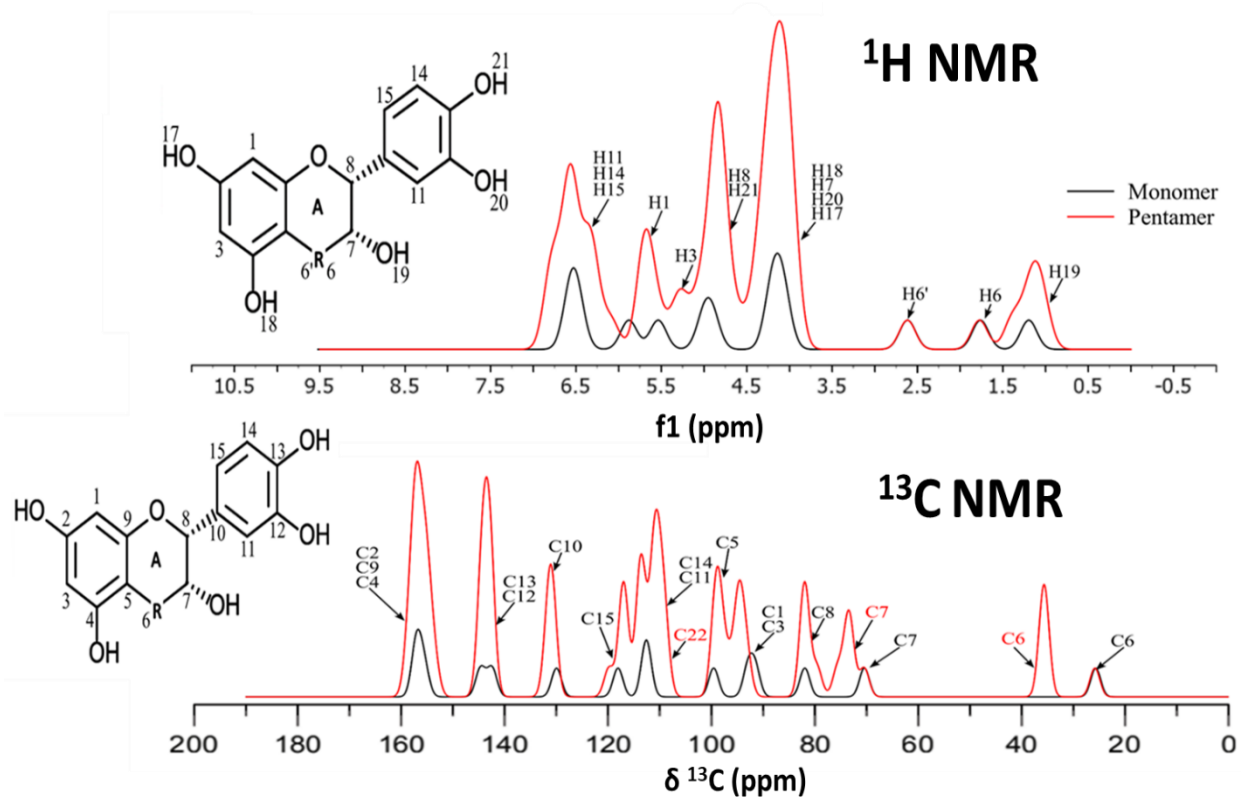

Figure 14: Theoretical ^{1}H-NMR & ^{13}C-NMR spectra of (-)-epicatechin monomer and pentamer (Paper IV).

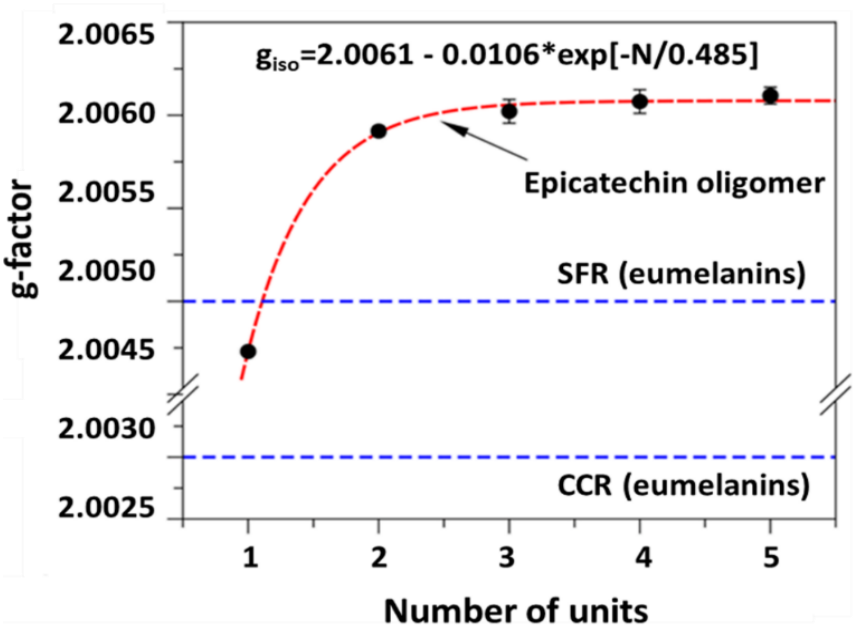

Figure 15: EPR simulation studies using (-)-epicatechin through density functional theory (DFT) (Paper IV).

Chapter 4: Conclusions and Future Perspectives

Most previously reported studies on date fruit phenolic compounds focused only on soluble phenolic compounds. However, this study is the first to present the LC-MS/MS analysis of hydrolyzable phenolic compounds in date fruits. Additional studies are necessary to understand the extractability of phenolic compounds present in a complex matrix, indicating the need for alternative chromatographic techniques, such as hydrophilic interaction liquid chromatography. Alternative easy and high throughput chemometrics-based methods should be considered because total antioxidant activity assays cannot accurately assess the antioxidant potential of phenolic compounds. The disagreement between these methods questions their reliability since the accuracy of an analytical method is confirmed by agreement between independent methods.

In this study, melanin was extracted from date fruits for the first time and demonstrated bioactivity. It can be used in different applications, including cosmetics, bioelectronics, and biotechnology (e.g., nanoparticles for food packaging and dying pigments). In addition, date fruit melanin can be extracted from date fruit cultivars and pomace that can be utilized in several applications. Advanced techniques, such as MALDI-TOF, are also needed to properly investigate high-molecular-weight trimers and above. In addition, polymeric proanthocyanidins may be partially extracted and still present in the discarded pulp. Further studies are necessary to determine the complete phenolic profile of date fruits due to the presence of proanthocyanidin and its various forms.

Date fruits are rich in soluble, hydrolyzable, and insoluble phenolic compounds that can be exploited for a wide range of functional and bioactive properties. Investigation of low-grade date fruits and their industrial waste can be an economical source of phenolic compounds. Further studies on hydrolyzable phenolic compounds are required because previously reported studies (*in vivo* and *in vitro*) were only conducted on soluble phenolic compound extracts. Environmentally friendly extraction methods for extracting melanin in its pure form are necessary. In addition, the coextraction of lignin and hemicellulose suggests further research on the development of separation techniques for melanin purification. The NMR and EPR studies of melanin indicate that date fruit melanin is an oligomeric polymer composed of monomeric units of (-)-epicatechin. However, the exact

structural composition of melanin is a challenge that requires further investigation. Comparative studies on the structural composition of melanin extracted from different date fruit cultivars will provide a better overview of its biosynthetic pathway and properties. Furthermore, this study provides new insight into the search for melanin in low-value date fruits and fruit processing waste to enhance its commercial feasibility and explore other extraction techniques. Investigations on polymeric forms of phenolic compounds present in date fruits, such as proanthocyanidins, lignin, and melanin, also require more in-depth analysis of efficient extraction techniques and characterization methods.

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List of Other Publications

Alam, M. Z., Al-Hamimi, S., Ayyash, M., Rosa, C. T., Yahia, E. M., Haris, S., Al-Marzouqi, A. H., & Kamal-Eldin, A. (2023). Contributing factors to quality of date (*Phoenix dactylifera* L.) fruit. *Scientia Horticulturae, 321*, 112–256. https://doi.org/10.1016/j.scienta.2023.112256

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UAEU DOCTORATE DISSERTATION NO. 2024:42

This dissertation is aimed to investigate the phenolic compounds in date fruits, mainly soluble and hydrolyzable compounds, and insoluble melanin. Soluble and hydrolyzable phenolic extracts have been investigated using UPLC-QTOF-MS/MS and UPLC-DAD. Melanin from date fruits was quantified and its physiochemical characteristics were explored. Therefore, this dissertation provides new insights into the phenolic compounds present in date fruits, particularly hydrolyzable phenolic compounds and melanin.

Muneeba Zubair Alam received her PhD in Food Science and Technology from the Department of Food Science, College of Agriculture & Veterinary Medicine at the United Arab Emirates University, UAE. She received her M.Phil. and B.Sc. in Food Science and Technology from University of Karachi, Pakistan.