



Gastrointestinal stability and bioactivity of propolis from diverse origins

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Abstract

Propolis is a chemically complex bee product whose biological properties depend on its botanical and geographical origin. However, little is known about how gastrointestinal digestion affects its phenolic profile and bioactivity. In this study, twelve propolis samples from eight countries were evaluated for phenolic and flavonoid contents, antioxidant capacity (FRAP, ABTS+•), and urease inhibition before and after simulated gastric digestion. RP-HPLC–PDA identified 26 phenolic compounds showing substantial compositional diversity. Turkish Bolu propolis retained the highest post-gastric FRAP value, while several samples (BBP, AFP) maintained or enhanced urease inhibition. PCA and HCA highlighted origin-dependent differentiation, identifying digestive stability as a key variable for functional potential.

Keywords Propolis · Gastrointestinal stability · Antioxidant activity · Urease inhibition · PCA · HCA

Introduction

Propolis is a resinous material produced by honey bees (*Apis mellifera*) through the mixing of beeswax, salivary secretions, and plant-derived exudates collected from buds, bark, and leaves near the hive. This complex biochemical matrix primarily functions as a structural and antimicrobial barrier that seals hive cavities and protects the colony against pathogens and environmental stressors. The colour and composition of propolis vary widely depending on the botanical and geographical sources of the collected resins, ranging from yellow and brown to green, red, and black [1]. Among global producers, Brazil is recognized for its botanical richness and the diversity of its propolis types, including red, brown, and green varieties [2]. Numerous factors such as floral source, climate, harvesting season, and bee species strongly influence the physicochemical profile and bioactivity of propolis extracts. To date, over 500 compounds have been identified, primarily phenolic acids, flavonoids, and terpenes, underscoring the remarkable chemical complexity of this natural product. Owing to its rich bioactive composition, propolis has gained substantial interest as a natural therapeutic and functional ingredient with antioxidant, antimicrobial, anti-inflammatory, and gastroprotective properties [3, 4]. Its potential applications in gastrointestinal disorders, including colitis, gastritis, and peptic ulcer disease, have been particularly noted [5, 6].

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Despite extensive research on its composition and pharmacological activities, the influence of gastrointestinal digestion on the stability, transformation, and bioaccessibility of phenolic compounds in propolis remains poorly understood. Moreover, few studies have compared the digestive behavior of propolis from distinct geographical origins. Understanding these changes is essential, since the bioactive potential of phenolics depends not only on their native concentration but also on their stability and accessibility during digestion.

We hypothesized that propolis from temperate regions would exhibit higher digestive stability. This is due to higher phenolic content, greater flavonoid diversity, and adaptation to seasonal stresses in their botanical sources, potentially enhancing resilience to gastrointestinal conditions compared to tropical counterparts. Therefore, this study aimed to evaluate the compositional diversity and digestive stability of twelve propolis samples from eight countries and identify phenolic markers related to bioactivity. As urease activity constitutes a key survival mechanism for *Helicobacter pylori* in the acidic gastric niche, inhibition of this enzyme is regarded as a functionally relevant target in the context of gastric physiology. Accordingly, assessing the stability of phenolic constituents and their associated bioactivities under simulated gastric conditions was considered a physiologically justified approach for investigating the potential functional role of propolis.

Materials and methods

Chemicals and reagents

All chemicals used in this study were of analytical grade. Phenolic acid standards were obtained from Sigma-Aldrich Chemie GmbH (Germany) and Merck (Darmstadt, Germany), while Trolox was supplied by AppliChem (Darmstadt, Germany). Folin–Ciocalteu's phenol reagent and

TPTZ were purchased from Fluka Chemie GmbH (Switzerland). Iron(III) chloride hexahydrate ($\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$), 2,4,6-Tris(2-pyridyl)-s-triazine (TPTZ), iron(II) sulfate heptahydrate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$), and ABTS $^{+\bullet}$ were obtained from Sigma-Aldrich (St. Louis, MO, USA). Sodium acetate, ferric chloride, urea, thiourea and glacial acetic acid were purchased from Merck. LC syringe filters (RC-membrane, 0.2 μm) were acquired from Sartorius Minisart RC 15 (Sartorius, Darmstadt, Germany).

Collection of propolis samples

Twelve propolis samples from diverse regions in eight countries were obtained as raw materials for analysis. The codes of the samples are as in Table 1 (Table 1; Fig. 1). Following collection, the samples were preserved at -20°C until subjected to analysis.

Extracts were prepared by mixing 3 g of propolis with 30 mL of 70% ethanol and shaking for 24 h at 200 rpm (Heidolph Promax 2020) and subsequently filtered through Whatman No. 1 filter paper, followed by a 0.45 μm membrane filter.

Total phenolic content

Total phenolic content (TPC) was quantification was performed according to the method described in [7], with minor modifications. Each 20 μL extract was reacted with 400 μL Folin–Ciocalteu's reagent (0.25 N), 400 μL sodium carbonate (7.5%), and 750 μL distilled water. Absorbance was measured at 765 nm (Thermo Scientific EvolutionTM 201, USA), and values were expressed as mg gallic acid equivalents per gram (mg GAE/g).

Total flavonoid content

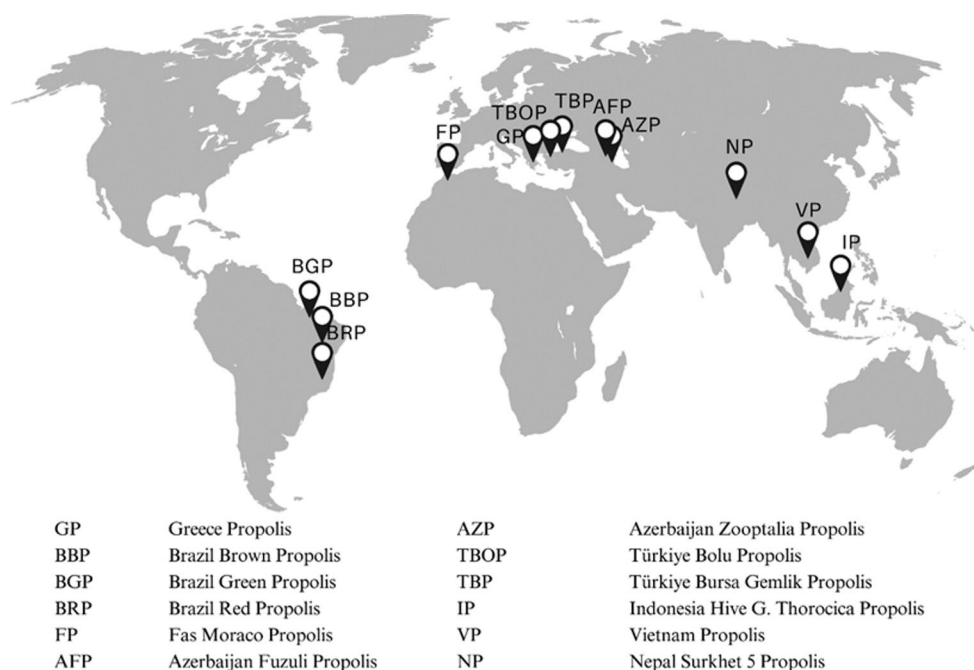
The total flavonoid content of the propolis extract prepared in 70% ethanol was determined according to the method described [8]. In this assay, 250 μL of the sample was mixed with 1.25 mL of methanol, 0.05 mL of 10% $\text{Al}(\text{NO}_3)_3$, and 0.05 mL of 1 M $\text{CH}_3\text{COONH}_4$. The reaction mixture was incubated for 50 min at room temperature, and the absorbance was subsequently determined at 415 nm. Results were expressed in terms of milligrams of quercetin equivalents per gram of sample.

Antioxidant activity of propolis samples

To evaluate the antioxidant activity of the propolis samples, the widely used FRAP and ABTS $^{+\bullet}$ assays were employed.

Table 1 Propolis samples, origin and year of harvest

Propolis Code	Origin	Season/Year
GP	Greece Propolis	Spring / 2024
BBP	Brazil Brown Propolis	Spring / 2024
BGP	Brazil Green Propolis	Spring / 2024
BRP	Brazil Red Propolis	Spring / 2024
FP	Fas Morocco Propolis	Spring / 2024
AFP	Azerbaijan Fuzuli Propolis	Spring / 2024
AZP	Azerbaijan Zootalia Propolis	Spring / 2024
TBOP	Türkiye Bolu Propolis	Spring / 2024
TBP	Türkiye Bursa Gemlik Propolis	Spring / 2024
IP	Indonesia Hive <i>G. Thorocica</i> Propolis	Spring / 2024
VP	Vietnam Propolis	Spring / 2024
NP	Nepal Surkhet 5 Propolis	Spring / 2024

Fig. 1 The codes of the samples

Ferric reducing/antioxidant power (FRAP) assay

Reducing power was determined using the ferric-reducing antioxidant power (FRAP) assay [9]. Propolis extracts (100 μ L) were incubated with freshly prepared FRAP reagent (Fe(III)-TPTZ, FeCl_3 , acetate buffer in 40 mM HCl, and 20 mM $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$) for 4 min at 25 $^\circ\text{C}$, and absorbance was recorded at 593 nm. A standard curve of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (31.25–1000 μM) was used, and results were expressed as $\mu\text{mol FeSO}_4 \cdot 7\text{H}_2\text{O}$ equivalents per g of sample.

ABTS $^{+ \cdot}$ radical scavenging capacity

The ABTS $^{+ \cdot}$ radical scavenging assay was carried out following the procedure of [10] with slight modifications. A stock solution of ABTS (7.4 mM) was prepared in ultrapure water and combined with 2.45 mM potassium persulfate to initiate radical cation (ABTS $^{+ \cdot}$) formation. The reaction mixture was kept in the dark at room temperature for 16–18 h to ensure complete oxidation. Prior to use, the ABTS $^{+ \cdot}$ solution was diluted with 5 mM phosphate buffer (pH 7.4) until the absorbance at 734 nm reached 0.70 ± 0.02 .

Six different concentrations were prepared from each propolis sample, and 2 mL of ABTS $^{+ \cdot}$ reagent, adjusted to an absorbance of 0.70, was added to each. After 5 min of incubation, absorbance was measured at 734 nm. The results were compared with the Trolox standard, and the SC_{50} values were expressed in mg/mL of extract.

In vitro urease inhibition of propolis

Urease, an enzyme responsible for catalyzing the degradation of urea into ammonia and carbon dioxide, was evaluated for its inhibition activity using the indophenol method [11, 12]. The assay measured the amount of ammonia formed as a result of enzyme–substrate interaction in a pH 8.2 buffer system containing urea. The produced ammonium ions were subsequently reacted with a phenol solution (1% phenol and 0.005% sodium nitroprusside) and an alkaline solution (0.5% NaOH and 0.1% sodium hypochlorite), resulting in the development of a blue colour complex. Thiourea was used as reference. Inhibition results were expressed as IC_{50} mg/mL.

RP-HPLC–PDA analysis of propolis samples

A total of 26 individual phenolic constituents were characterized in the propolis samples through RP-HPLC–PDA analysis. The phenolic content of the samples was determined according to the validated method described by Kara and Birinci [13]. The chromatogram of phenolic standards is as in Fig. 2.

High-performance liquid chromatography (HPLC) analysis was performed using a Shimadzu LC 20AT system equipped with a photodiode array (PDA) detector. Separation was achieved on a 250 mm $\times$ 4.6 mm analytical column with a 5 μm particle size, supplied by GL Sciences. ¹³ A gradient elution program was employed, using two mobile phases: 70% acetonitrile in ultrapure water (phase A) and 2% acetic acid in water (phase B). The flow rate

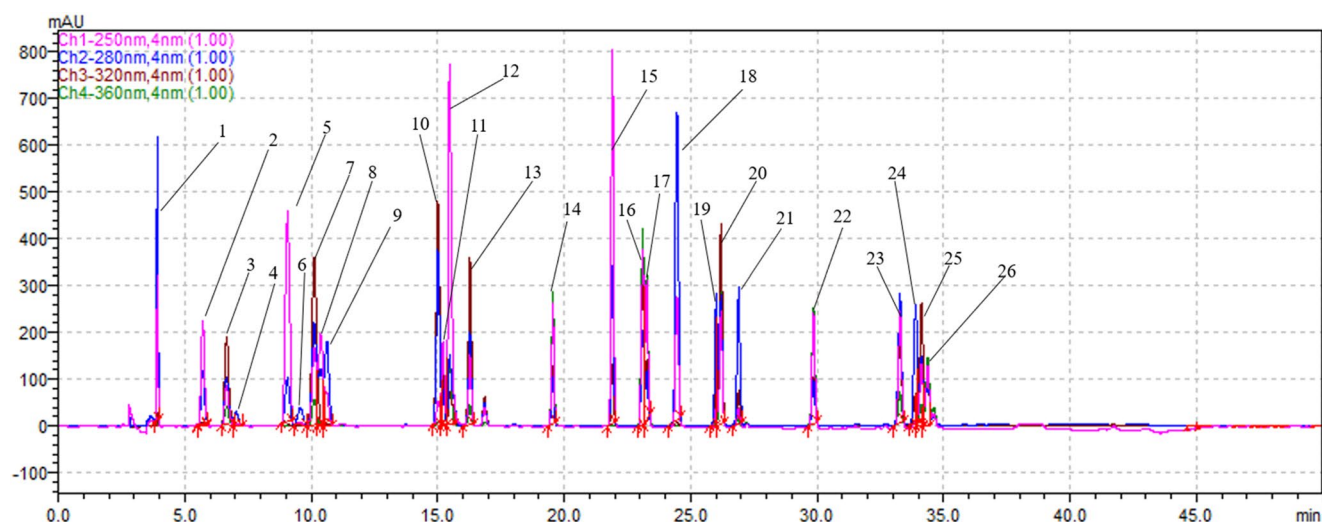


Fig. 2 Phenolic Standard Chromatogram. (1) Gallic acid, (2) Protocatechuic acid, (3) Chlorogenic acid, (4) Catechin hydrate, (5) *p*-OH Benzoic acid, (6) Epicatechin, (7) Caffeic acid, (8) Vanillic acid, (9) Syringic acid, (10) *p*-Coumaric acid, 11. Rutin, 12. Ellagic acid, 13.

Ferulic acid, 14. Myricetin, 15. Daidzein, 16. Luteolin, 17. Quercetin, 18. *t*-Cinnamic acid, 19. Naringenin, 20. Apigenin, 21. Hesperetin, 22. Rhamnetin, 23. Chrysin, 24. Pinoembirin, 25. CAPE, 26. Galangin

was maintained at 1 mL/min, with an injection volume of 20 μ L for both samples and standards. The column temperature was kept at 30 $^{\circ}$ C throughout the analysis. Detection was carried out over the 250–360 nm wavelength range, with chromatograms monitored at 250, 280, 320, and 360 nm [13].

Ethanol solvent was evaporated from the pre-digestion samples. The pH of the post-gastric samples was adjusted to 2 before extraction. Liquid–liquid extraction was performed twice for all samples using the same solvent system. First with 10 mL and subsequently with 5 mL of diethyl ether, at room temperature with shaking at 200 rpm for 15 min. The procedure was repeated using ethyl acetate. After each extraction, the organic phase was collected in a separate flask, and the solvent was removed under reduced pressure at 40 $^{\circ}$ C. The resulting residue was dissolved in 2 mL of HPLC-grade methanol, filtered through a 0.45 μ m membrane filter, and subsequently injected into the RP-HPLC–PDA system for analysis. No additional liquid–liquid extraction was performed specifically for post-digestion samples; both undigested and digested extracts were prepared for chromatographic analysis using the same solvent system and identical sample preparation conditions to ensure analytical comparability.

In vitro digestion procedure

To evaluate the potentially bioaccessible fractions associated with phenolic content, antioxidant capacity, and urease inhibitory activity, propolis extracts were subjected to an in vitro simulated gastric digestion procedure, modified

by Değirmenci et al. [14] based on the protocol originally described by McDougall et al. [15].

Post-gastric (gastric phase only)

3 mL of the sample extract was diluted with 15 mL of PBS solution. Then, the pH was adjusted to 2 using 1 M HCl. After adding 1.5 mL of 315 U mL⁻¹ pepsin, the incubation of the mixture was performed at 37 $^{\circ}$ C and 100 rpm for 2 h, corresponding to the stomach digestion. Following incubation, the samples were centrifuged and the resulting supernatants were collected as extracts for subsequent analyses. The extracts were stored at -20° C until further use (post-gastric, PG).

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics, version 26. Correlations among antioxidant parameters and urease activity measured before and after digestion were evaluated to characterize inter-variable relationships. Dimensionality reduction and unsupervised clustering of the samples were performed using Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA), respectively.

Results and discussion

TPC, TFC, and antioxidant activity of propolis samples

Twelve propolis samples from eight countries were evaluated for total phenolic content (TPC), total flavonoid content (TFC), and antioxidant capacity (FRAP and ABTS assays) (Table 2). Significant compositional and functional diversity was observed among the samples. GP exhibited the highest TPC (361.78 mg GAE/g), while FP contained the highest TFC (75.70 mg QE/g). In contrast, VP presented the lowest phenolic content (7.88 mg GAE/g) and flavonoid (2.83 mg QE/g) levels.

GP, characterized by high TPC and TFC, also displayed the strongest ABTS radical-scavenging activity, indicating the presence of highly redox-active flavonoids. Conversely, VP showed the weakest ferric-reducing antioxidant power (53.10 $\mu\text{mol FeSO}_4 \cdot 7 \text{H}_2\text{O/g}$), consistent with its low phenolic content. A study conducted in Indonesia reported that the TPC of propolis samples collected from 10 different locations varied between 50.03 and 98.03 mg GAE/g, whereas the TFC ranged from 0.70 to 57.76 mg QE/g [16], which is comparable to the Indonesian sample analyzed here.

The observed differences align with previous studies reporting substantial variability in the phenolic composition of propolis depending on floral and geographical sources [17, 18]. Such variability likely reflects distinct plant exudates available to bees, as well as regional climatic influences on resin secretion. Overall, these results confirm that propolis is a chemically heterogeneous material whose antioxidant potential is strongly origin-dependent.

The FRAP assay supported the compositional findings, confirming the antioxidant potential of phenolic-rich

samples. VP demonstrated the lowest ferric-reducing power (53.10 $\mu\text{mol FeSO}_4 \cdot 7 \text{H}_2\text{O/g}$), consistent with its low TPC and TFC. Turkish (Bursa and Bolu) and Brazilian propolis exhibited moderate FRAP activity, in line with their intermediate phenolic contents. Notably, GP not only showed high phenolic and flavonoid levels but also demonstrated the strongest ABTS radical-scavenging activity, suggesting that its bioactive profile may be particularly rich in highly reactive phenolic compounds.

In vitro urease enzyme inhibition of propolis samples

The urease inhibitory activities of the twelve propolis samples are summarized in Table 2. IC_{50} values ranged from 0.86 mg/mL (FP) to undetectable levels (VP, NP). Moroccan propolis demonstrated the strongest urease inhibition, followed by Greek and Brazilian red propolis.

A study conducted on propolis samples collected from different regions of Georgia in 2020 reported urease inhibitory IC_{50} values ranging from 0.004 to 1.485 mg/mL [19]. In another study, Turkish propolis was reported to exhibit urease inhibitory activity with an IC_{50} value of 3.78 mg/mL [20]. The difference between our findings and previous reports may be explained by differences in the geographical origin, plant sources, and chemical profiles of the propolis samples, which are known to significantly influence their bioactive properties.

Phenolic content by RP-HPLC-PDA

Prior to digestion, propolis samples were analyzed by RP-HPLC–PDA for 26 standard phenolic compounds; the samples coded FP, GP, AFP, AZP, TBOP, TBP, and BGP

Table 2 TPC, TFC, ABTS ABTS⁺⁺, FRAP, and urease enzyme inhibition of propolis samples

No.	Sample	TPC mg GAE/g	TFC mg QE/g	FRAP ($\mu\text{molFeSO}_4 \cdot 7\text{H}_2\text{O/g}$)	ABTS ⁺⁺ SC ₅₀ mg/mL	Urease IC ₅₀ mg/mL
1	GP	361.78±1.66 ^a	10.72±0.42 ^c	1678.70±14.48 ^b	0.25±0.00 ^a	2.71±0.183 ^b
2	BBP	206.87±6.07 ^d	38.31±4.35 ^c	1154.61±57.57 ^d	0.47±0.01 ^c	8.68±0.75 ^c
3	BGP	238.03±1.54 ^c	45.67±1.42 ^b	1275.16±38.10 ^c	0.84±0.07 ^d	9.72±0.56 ^c
4	BRP	221.45±1.54 ^c	5.18±0.42 ^e	905.75±41.88 ^d	0.48±0.02 ^c	2.49±0.11 ^b
5	FP	319.21±2.85 ^b	75.70±0.54 ^a	2219.71±14.46 ^a	0.69±0.04 ^d	0.86±0.08 ^a
6	AFP	275.49±8.06 ^c	28.54±0.32 ^d	751.21±3.01 ^d	0.37±0.01 ^b	7.30±0.01 ^d
7	AZP	168.42±11.51 ^d	43.36±0.22 ^b	1337.66±13.78 ^c	0.50±0.00 ^c	4.60±0.53 ^c
8	TBOP	127.95±1.75 ^d	34.02±1.50 ^c	679.00±5.77 ^d	0.60±0.01 ^d	5.17±0.33 ^d
9	TBP	84.38±0.33 ^e	27.580±0.758 ^d	1333.76±8.45 ^c	1.07±0.04 ^c	7.02±1.99 ^d
10	IP	31.87±0.15 ^e	10.83±0.28 ^e	231.09±7.29 ^e	1.24±0.31 ^e	4.50±0.01 ^c
11	VP	7.89±0.49 ^e	2.83±0.17 ^e	53.10±0.96 ^e	16.30±0.22 ^e	not detected.
12	NP	13.56±0.53 ^e	4.86±0.18 ^e	106.22±0.86 ^e	9.93±0.20 ^e	not detected.
	Trolox				0.002±0.000	
	Thiourea					0.014±0.00

Means followed by the same letter within each column are not significantly different according to one-way analysis of variance (ANOVA) followed by Tukey's post hoc test ($p < 0.05$)

exhibited a greater number of phenolic constituents compared with the other propolis samples (Table 3). In the study conducted by Touzani et al. [21] on propolis samples obtained from Fas different regions, pinocembrin was identified as the major component. In the present study, pinocembrin was likewise identified as the major component in the FP sample, and these results are consistent with the literature. The phenolic compounds identified for TBOP and TBP in this study show similarity to previous findings and are consistent with the literature [22]. The diversity of phenolic constituents detected in the IP, VP, and NP samples is significantly lower than that of propolis samples sourced from other countries.

Changes of TPC, and antioxidant activity in propolis after in vitro digestion

The post-gastric digestive evaluation of propolis samples from different geographical origins revealed marked variations in both total phenolic content (TPC) and antioxidant capacity (FRAP) Table 4. After digestion, most samples showed a decline in both phenolic content and antioxidant capacity. TBOP retained the highest TPC (91.0 mg GAE/g) and FRAP (419.7 $\mu\text{mol Fe}^{2+}$ /g), indicating high phenolic stability. In contrast, VP and NP lost almost all detectable spectrophotometrically phenolics, suggesting high susceptibility to degradation. This aligns with findings by Turgut et al. [23], who reported a decrease from 91% to 87% in phenolic compounds during simulated gastric digestion, indicating a substantial retention of bioactive compounds. IP showed minimal TPC (2.20 mg GAE/g) and no detectable FRAP activity. This is consistent with observations by Yesiltas et al. [24] who found that the bioaccessible fraction of propolis was minimal, with total phenolic content at 2.0 mg GAE/g and antioxidant activity at 19.6 mg TE/g.

FRAP-measured antioxidant capacity showed a different trend compared to TPC. Despite its low TPC, TBP exhibited the highest FRAP value (490.83 $\mu\text{mol Fe}^{2+}$ /g), indicating that non-phenolic antioxidants or highly bioactive phenolic subgroups may significantly contribute to post-digestive activity. TBOP, BBP, and BGP also maintained high FRAP levels (419.71, 429.74, and 401.54 $\mu\text{mol Fe}^{2+}$ /g, respectively), whereas IP showed no detectable FRAP activity, consistent with its low TPC.

Post-gastric, a general decline in bioactive parameters was observed. TPC values decreased sharply across most samples, with reductions ranging from 6.9% (IP) to 71.16% (TBOP). A similar decreasing trend was noted in FRAP, with the largest loss observed in TBOP (61.84%) and the lowest in FP (9.79%). The digestive stability of phenolics varied widely, ranging from 6.9% (IP) to 71.16% (TBOP). Samples such as TBOP (71.16%), BGP (26.33%), and BBP

(24.72%) exhibited relatively high phenolic stability after digestion, while FP (6.95%) and AFP (6.89%) showed the lowest retention. This indicates that the phenolic compounds in certain propolis types are more resistant to digestive degradation, potentially due to their structural properties or the protective effect of the propolis matrix. Bioaccessible FRAP values followed a similar trend. The highest retention was recorded in TBOP (61.84%) and BBP (37.23%), whereas FP (9.79%) and GP (12.74%) exhibited the lowest. Interestingly, FP, despite having one of the highest FRAP values before digestion, showed poor retention, suggesting that its antioxidant constituents are highly sensitive to digestive conditions. Table 4.

Changes of urease enzyme inhibition in propolis after in vitro digestion

Following post-gastric digestion, notable shifts in urease inhibition were observed (Table 4). In some samples, such as GP and TBOP, IC_{50} values increased significantly, indicating reduced inhibition. The decrease in urease inhibition can be attributed to the reduction in phenolic constituents in propolis samples after gastric digestion. Conversely, certain samples maintained or even enhanced their inhibitory potential after digestion. These are BBP and AFP samples. These findings indicate that the urease inhibitory activity of propolis is influenced not only by geographical origin but also by the stability of its bioactive compounds under gastric conditions. Previous studies have demonstrated that the phenolic composition of propolis, particularly flavonoids and phenolic acids, plays a crucial role in urease inhibition [25]. The strong activity of FP and BRP prior to digestion may therefore be attributed to their higher phenolic content. However, the dramatic reduction in activity following digestion suggests that these compounds are susceptible to degradation or chemical transformation in acidic environments, which diminishes their inhibitory capacity. In contrast, the stability or enhanced activity observed in BBP and AFP may be related to their unique phenolic contents. Brazilian brown propolis is particularly rich in artepillin C and prenylated phenolic acids, compounds reported to exhibit greater stability under gastrointestinal conditions [26, 27]. Such differences highlight that the bioefficacy of propolis cannot be generalized but rather depends on both composition and digestion-related transformations. AFP displayed not only resistance to degradation but also an enhanced urease inhibitory capacity following digestion, indicating that digestive processes may liberate active metabolites with stronger enzyme-binding affinity. Such findings underscore the importance of considering not only the native composition but also the gastrointestinal of bioactive compounds when evaluating their functional potential. Overall, the

Table 3 Phenolic content of propolis samples before and after digestion

Standards	PrA	ChA	CaH	BeA	Epi	CaA	Ru	EA	CA	FA	Qu	CiA	Ap	Rh	Chr	Pi	CAP	Ga
GP	<LOQ	—	—	3.60	—	233.05	—	—	93.18	146.95	—	—	117.73	—	2637.69	1417.80	903.77	1714.37
GP postgastric	0.61	—	—	0.91	—	52.04	—	—	16.39	26.39	—	—	0.88	—	6.08	8.76	3.71	4.33
BBP	16.32	1.22	—	12.99	—	87.45	—	—	632.85	47.66	—	—	—	—	—	—	—	—
BBP postgastric	5.23	0.70	—	4.12	—	29.96	—	—	178.16	13.24	—	—	—	—	—	—	—	—
BGP	10.55	178.08	—	9.30	—	65.90	—	—	859.36	26.69	—	—	—	—	148.07	—	—	—
BGP postgastric	3.37	96.09	—	2.81	—	25.12	—	—	253.65	17.20	—	—	—	—	4.08	—	—	—
BRP	21.51	—	8.64	—	<LOQ	—	—	4.29	—	—	—	—	—	—	—	87.77	—	—
BRP postgastric	13.31	0.55	2.00	—	6.23	0.51	—	2.65	—	—	—	—	—	—	—	1.51	—	—
FP	<LOQ	—	—	—	—	278.47	—	—	9.94	13.72	132.31	—	177.26	399.76	1891.41	4173.30	460.37	2261.51
FP postgastric	0.54	—	—	—	—	97.42	—	—	2.72	8.33	8.22	—	1.40	3.81	62.40	37.78	3.65	7.4
AFP	—	2.51	—	3.94	—	214.16	—	—	162.62	28.82	112.01	127.08	108.69	—	1145.87	1160.44	426.98	1256.68
AFP postgastric	0.37	0.75	—	1.05	—	33.34	—	3.38	—	6.43	3.67	11.12	0.73	—	3.65	7.06	2.03	3.41
Sample μg phe- nolic /mL sample																		
AZP	—	2.99	—	4.74	—	181.41	—	—	140.04	28.12	94.23	112.98	79.50	—	993.61	1036.15	335.40	1062.89
AZP postgastric	1.01	0.19	—	1.85	—	106.05	—	—	72.29	—	10.08	—	1.90	—	6.09	17.56	4.41	5.83
TBOP	<LOQ	—	—	6.37	—	271.78	—	—	301.87	858.30	43.45	159.62	82.87	—	1071.62	1193.99	410.51	882.04
TBOP postgastric	0.37	—	—	2.28	—	60.25	—	—	57.11	153.59	2.05	16.45	0.71	—	4.16	13.61	3.70	3.29
TBP	0.91	<LOQ	—	1.10	—	139.22	—	6.24	52.61	24.42	44.84	60.69	68.62	—	800.87	999.09	784.23	784.23
TBP postgastric	0.65	0.34	—	0.60	1.41	31.42	—	0.51	12.82	6.40	4.93	10.26	1.98	—	8.35	19.20	75.77	8.33
IP	3.03	—	—	0.56	—	—	1.80	—	—	—	—	—	—	—	—	—	—	—
IP postgastric	0.42	—	—	0.53	—	—	—	—	—	—	—	—	—	—	—	—	—	—
VP	—	—	—	—	—	—	—	18.53	—	—	13.48	—	—	—	—	—	—	—
VP postgastric	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
NP	—	—	—	—	—	<LOQ	—	11.63	—	—	—	—	—	—	—	—	—	—
NP postgastric	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

not detected. Detected and Undetected Phenolic Compounds (Abbreviations and Full Names) - (Gallic acid: GA, Protocatechuic Acid: PCA, Chlorogenic Acid: ChA, Catechin Hydrate: CaH, *p*-OH Benzoic Acid: BeA, Epicatechin: Epi, Caffeic Acid: CaA, Syringic Acid: SyA, Vanillic Acid: VA, Rutin: Ru, Ellagic Acid: EA, *p*-Coumaric Acid: CA, Ferulic Acid: FA, Myristin: My, Daidzein: Da, Luteolin: Lu, Quercetin: Qu, *t*-Cinnamic Acid: CiA, Naringenin: Na, Apigenin: Ap, Hesperetin: He, Rhamnetin: Rh, Chrysin: Chr, Pinocembrin: Pi, CAPE: CAP, Galangin: Ga

Table 4 Post Gastric-TPC, Post Gastric-FRAP, and Post Gastric-Urease Enzyme Inhibition of Propolis Samples

Sample	Post Gastric Digestive TPC mg GAE/g	BI TPC%	Post Gastric Digestive FRAP ($\mu\text{molFeSO}_4 \cdot 7\text{H}_2\text{O/g}$)	BI FRAP %	Post Gastric Digestive Urease IC ₅₀ mg/mL	Potency retention (%)
GP	59.95±0.64	16.56	213.93±1.50	12.74	5.59±0.18	48.48
BBP	51.14±0.15	24.72	429.74±6.68	37.23	7.03±0.03	52.65
BGP	62.672±0.00	26.33	401.54±2.03	31.49	15.51±1.31	75.59
BRP	18.11±0.85	8.18	123.58±3.38	13.65	8.22±0.002	49.88
FP	22.19±0.56	6.95	217.49±1.18	9.79	10.94±0.33	7.86
AFP	18.97±0.03	6.89	141.13±0.58	18.79	6.29±0.10	116.06
AZP	28.52±0.49	16.93	272.87±1.50	20.39	5.11±0.276	90.02
TBOP	91.03±0.10	71.16	419.71±1.34	61.84	16.02±1.20	32.27
TBP	14.44±0.12	17.11	490.83±0.00	36.80	8.31±0.097	84.48
IP	2.20±0.02	6.90	Not detected.	Not detected.	13.22±0.15	34.04
VP	Not detected.	Not detected.	Not detected.	Not detected.	Not detected.	Not detected.
NP	Not detected.	Not detected.	Not detected.	Not detected.	Not detected.	Not detected.

*BI (%): Bioactivity index, expressing the relative change in biological activity after simulated gastric digestion compared to the undigested sample. Potency retention (%): Percentage of biological activity retained after digestion, calculated relative to the activity of the undigested extract

Table 5 Pearson correlation of TPC, TFC, FRAP, ABTS+, Urease Post TPC, Post FRAP, Post Urease of propolis samples

	TPC_pre	TFC	FRAP_pre	ABTS	Urease_pre	TPC_post	FRAP_post	Urease_post
TPC_pre	1	0.342	0.283	− 0.230	0.523	− 0.137	0.351	0.474
TFC		1	0.734**	− 0.487	0.329	− 0.224	0.555	0.476
FRAP_pre			1	− 0.632*	0.203	− 0.346	0.560	0.305
ABTS				1	− 0.593*	− 0.117	− 0.566	− 0.665*
Urease_pre					1	0.030	0.709**	0.531
TPC_post						1	− 0.370	0.343
FRAP_post							1	0.501
Urease_post								1

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

results demonstrate that while simulated gastric digestion diminishes the antioxidant and phenolic content of propolis, certain extracts retain or even enhance their bioactivity against urease. These findings provide valuable insights into the functional stability of propolis under physiological conditions, highlighting promising candidates for nutraceutical applications. Pearson correlation analysis revealed notable associations among the bioactive parameters of propolis (Table 5). A strong positive correlation between TFC and FRAP ($r = 0.734$, $p < 0.01$) indicated that flavonoids are major contributors to the ferric-reducing antioxidant capacity. Similarly, TPC_pre correlated with Urease_pre ($r = 0.523$), suggesting that phenolic compounds influence enzyme inhibition through metal-binding and redox mechanisms.

A considerable negative correlation between FRAP and ABTS ($r = -0.632$, $p < 0.05$) reflected the distinct reaction principles of these assays. Post-gastric, Urease_post correlated with FRAP_post ($r = 0.501$), implying that antioxidant resilience and enzyme inhibition share structurally stable phenolic determinants. Overall, these relationships demonstrate that both antioxidant and urease-inhibitory activities

are primarily governed by flavonoid content and the digestive stability of phenolic compounds.

Changes of phenolic compounds in propolis after in vitro digestion

Following digestion, a decrease in phenolic constituents was observed in nearly all samples. Table 3. The chemical composition of propolis is intricately linked to the geographical origin, botanical diversity, and climatic conditions of the region [28]. As hypothesized in the introduction, propolis from temperate regions (e.g., BBP and AFP) exhibited higher digestive stability, likely due to their higher phenolic content and greater flavonoid diversity adapted to seasonal stresses. This is supported by the lower percentage variations in phenolic compounds post-gastric in these samples (e.g., only 20–30% loss in BBP). The decrease in phenolic compounds and antioxidant activity observed after gastric digestion may be associated with acid-induced structural transformations, oxidative reactions, and changes in compound solubility or extractability under simulated gastric conditions [29]. Low pH may promote structural

modifications and oxidative reactions affecting certain phenolic compounds, including flavonoids such as quercetin and phenolic acid derivatives such as caffeic acid and CAPE, which may contribute to reduced radical-scavenging capacity [27, 30]. Additionally, the formation of phenolic–protein complexes lower solubility and bioaccessibility [14]. Oxidative conversion to quinone-like structures and limited release from the waxy propolis matrix further diminish antioxidant capacity.²³ However, samples rich in lipophilic and acid-stable compounds such as pinocembrin and galangin (e.g., TBOP, TBP) showed higher stability, indicating their resistance to gastric degradation [27].

A more detailed examination of the chromatographic data provides additional insight into the antioxidant behavior of the samples. Propolis types characterized by high levels of flavonoid aglycones such as pinocembrin, galangin, chrysin, and CAPE generally exhibited stronger antioxidant capacity and greater post-gastric stability. These compounds are relatively lipophilic and structurally less susceptible to acid hydrolysis, which may explain the higher retention of FRAP activity observed in samples such as TBOP and BBP. In contrast, samples richer in phenolic acids showed greater reductions following digestion, consistent with the known acid sensitivity of these compounds. Thus, differences in antioxidant retention after digestion appear to be linked not only to total phenolic content but also to the structural stability of specific phenolic subclasses.

The spectrophotometric assays used in this study (TPC, TFC, FRAP, and ABTS^{•+}) provide general indicators of reducing capacity and antioxidant potential and were

applied as complementary approaches alongside chromatographic profiling. Urease inhibition was included as a targeted functional parameter because urease is a key enzyme associated with the gastric survival of *H. pylori*, making it a biologically relevant endpoint under simulated gastric conditions. Accordingly, post-digestion analyses were limited to selected chemical and functional parameters in order to evaluate the stability and persistence of representative bioactivities, rather than to provide an exhaustive assessment of all possible biological effects.

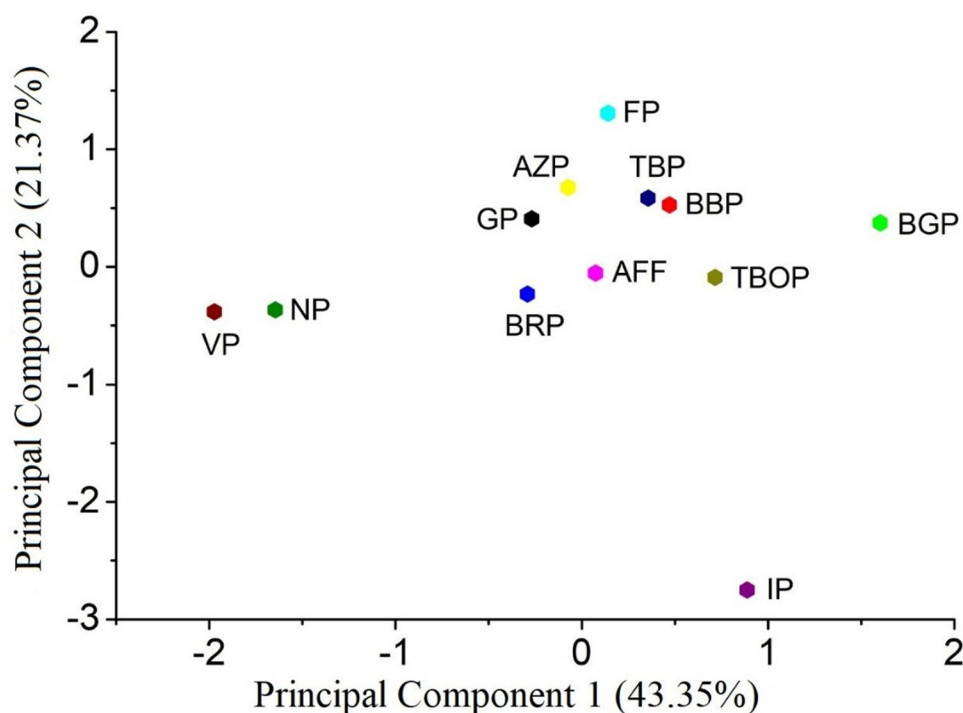
Multivariable analysis

Principal component analysis (PCA)

To elucidate the distribution patterns of the propolis samples according to the evaluated parameters, principal component analysis (PCA) was employed (Figs. 3 and 4). In the present study, this multivariate approach was used as an exploratory tool to assess general compositional and functional differences among propolis samples and was not intended to provide definitive classification according to botanical origin. This multivariate statistical approach enables the extraction of meaningful information from complex datasets by summarizing the overall variance into a limited number of principal components, thereby enhancing the interpretability of underlying relationships among variables [30].

The post-gastric parameters (TPC_post, FRAP_post, Urease_post) occupied a notable position in the PCA loading plot, underscoring the critical importance of gastrointestinal

Fig. 3 Score plot of the propolis samples



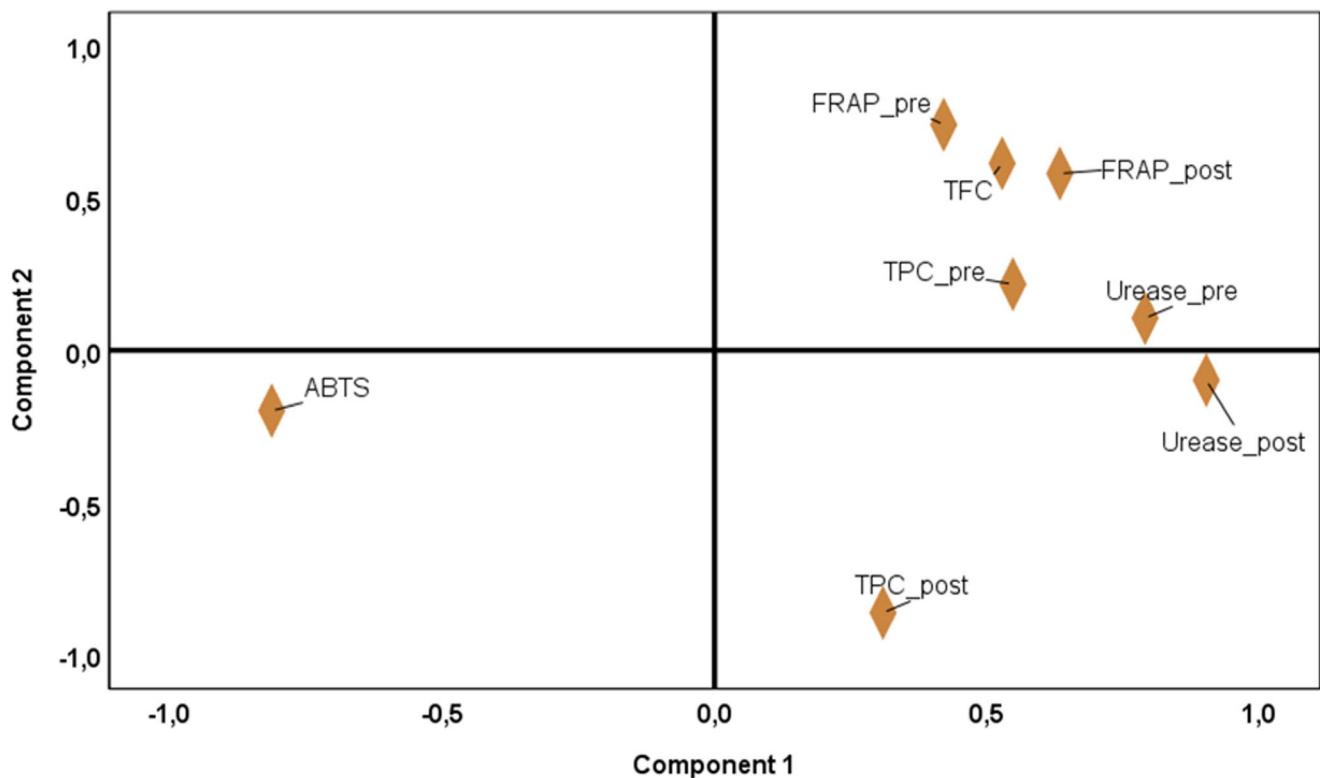


Fig. 4 Loading plot of PC1 and PC2

stability in evaluating the actual physiological effects of propolis after oral intake. In particular, the TBOP, TBP, BBP, and AFP samples either retained high post-gastric phenolic digestive stability and antioxidant capacity or even enhanced their urease-inhibitory activity. These findings suggest that these propolis types are more resilient to gastrointestinal conditions and therefore may represent promising candidates for nutraceutical or functional food applications.

Conversely, samples such as VP and NP, characterized by low phenolic content and reduced antioxidant capacity, highlight that not all propolis types exhibit the same degree of bioactivity, emphasizing the importance of source selection in product development. Furthermore, the distinct separation of BGP and IP suggests that these propolis types may harbor unique chemical constituents, potentially contributing to specific bioactivities not observed in other propolis varieties.

Hierarchical cluster analysis (HCA)

Hierarchical cluster analysis (HCA) grouped the twelve propolis samples into three main clusters based on their similarity patterns (Fig. 5).

The hierarchical cluster analysis (HCA) dendrogram presented in Fig. 5 classified the twelve propolis samples into three distinct main clusters based on their chemical

composition and bioactivity profiles: This cluster 1 comprised the Vietnam (VP) and Nepal (NP) propolis samples. These two samples clustered together at the lowest rescaled distance, indicating a high degree of similarity in both chemical composition and bioactivity. This similarity was consistent with their relatively low total phenolic content (TPC) and antioxidant capacity. The clustering suggests that propolis collected from neighboring tropical regions may share common chemical traits due to similar climatic conditions and botanical sources.

Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) revealed that propolis samples differ according to their geographical origin, with digestive stability emerging as a key discriminating factor. The first principal component (PC1), accounting for 45% of the total variance, was mainly associated with pre-digestion total phenolic content (TPC) and ferric reducing antioxidant power (FRAP), effectively separating Greek and Turkish samples from Vietnamese ones. This separation is likely due to the higher content of phenolic compounds with greater oxidative stability, such as galangin, in Greek and Turkish propolis. HCA further highlighted sub-clusters related to post-gastric phenolic stability, suggesting that environmental factors like climate and soil composition influence these differences.

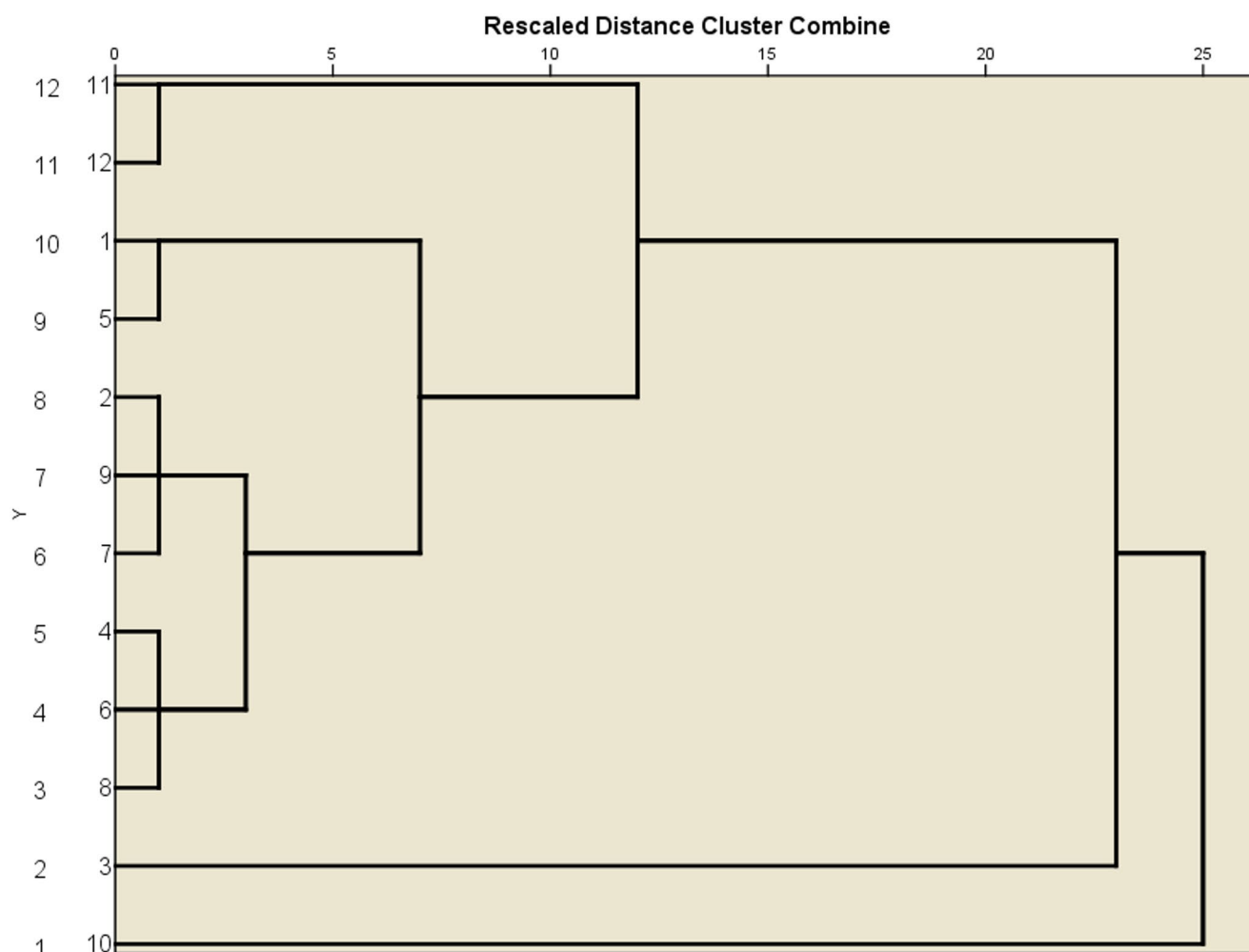


Fig. 5 The HCA dendrogram according to the TPC, TFC, FRAP, ABTS+•⁺, Urease, Post TPC, Post FRAP, Post Urease of propolis samples

The second cluster was more heterogeneous and could be further divided into two sub-clusters. The first sub-cluster included Brazilian red propolis (BRP), Azerbaijani Fuzuli propolis (AFP), and Turkish Bolu propolis (TBOP), while the second sub-cluster consisted of Greek (GP) and Moroccan propolis (FP). GP exhibited the highest TPC, whereas FP showed the highest total flavonoid content (TFC) among all samples, characterizing this cluster as rich in phenolic and flavonoid compounds. These samples demonstrated strong antioxidant activity and notable urease inhibition prior to digestion, reflecting the contribution of their abundant bioactive constituents. Although their geographical origins differ, the clustering indicates that their high phenolic and flavonoid levels drive similar bioactive properties, with only minor variations attributable to regional factors.

The third cluster included only Brazilian green propolis (BGP) and Indonesian propolis (IP), which separated from the other groups at a substantially higher rescaled distance, forming a clearly distinct cluster. This pronounced separation highlights that BGP and IP differ considerably from the

other propolis samples in terms of phenolic composition, antioxidant capacity, and urease-inhibitory potential. In particular, the unique chemical profile of BGP characterized by specific components such as artepillin C likely accounts for this divergence. These findings further underline the broad chemical diversity of propolis influenced by botanical origin and environmental factors.

Conclusion

This study demonstrates that the biological activity and phenolic composition of propolis are highly dependent on its geographical origin and botanical sources. Among the twelve propolis samples evaluated, Greek and Moroccan propolis exhibited superior total phenolic and flavonoid contents, respectively, while Vietnamese propolis showed the lowest bioactive potential across most parameters. Simulated gastric digestion caused a substantial loss of phenolic constituents and antioxidant capacity in most samples,

yet some, such as Turkish Bolu (TBOP) and Turkish Bursa (TBP) propolis, retained notable phenolic digestive stability and antioxidant potential. Notably, BBP and AFP preserved or even enhanced their urease inhibitory activity following digestion, suggesting that digestive processes can release metabolites with improved bioactivity.

Multivariate analyses (PCA and HCA) highlighted clear clustering patterns that reflect the influence of chemical diversity and digestive stability on functional properties. These findings underscore the importance of considering both the native composition and the digestive transformation of propolis when assessing its nutraceutical potential. Future studies focusing on the structural elucidation of digestion-resistant or digestion-enhanced compounds may provide deeper insight into the therapeutic value of specific propolis types. The reduced urease inhibition likely resulted from the degradation of phenolic constituents during gastric digestion.

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Author contributions Zehra Can contributed to conceptualization, methodology, investigation, formal analysis, writing – original draft; Zeynep Berin Çelebi contributed to methodology, formal analysis, Erol Tunca contributed to writing – review & editing, writing – original draft, and data curation, visualization. Sevgi Kolaylı contributed to Writing – review & editing, Writing – original draft. Sedat Sevin contributed to resources; Hidayet Tutun contributed to resources.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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