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LC–MS/MS-Based Identification and ADMET Profiling of Vitamin and Antioxidant Compounds from *Tenebrio molitor* with Antibacterial and Antibiofilm Activities Against Foodborne Pathogens

Gıda Kaynaklı Patojenlere Karşı Antibakteriyel ve Antibiyofilm Aktiviteleri Olan *Tenebrio molitor*'dan Elde Edilen Vitamin ve Antioksidan Bileşiklerin LC–MS/MS Tabanlı Tanımlanması ve ADMET Profili Oluşturulması

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ABSTRACT

Edible insects have been highlighted as an alternative source for functional food formulations. *Tenebrio molitor*, has been reported to be a more acceptable insect to humans. This study aimed to identify vitamins and antioxidant compounds present in *T. molitor* larvae by LC-MS/MS analysis. These compounds were analyzed for their Absorption, Distribution, Metabolism, Excretion, Toxicological (ADMET) profiles. Antibacterial and antibiofilm potential of extracts of *T. molitor* larvae against several foodborne pathogens were determined. The results demonstrated that high abundance vitamin B1 and vitamin B2 as vitamins, and quercetin, luteolin, and apigenin as antioxidant compounds. The extracts showed high levels of antibiofilm activity. Functional food ingredients can be analysed by computational analyses in the food R&D process.

Key Words
Tenebrio molitor, ADMET, LC-MS/MS, antibiofilm.

ÖZ

Yenilebilir böcekler, fonksiyonel gıda formülasyonları için alternatif bir kaynak olarak öne çıkmaktadır. *Tenebrio molitor*'ün insanlar için daha kabul edilebilir bir böcek olduğu bildirilmiştir. Bu çalışma, LC–MS/MS analizi kullanarak *T. molitor* larvalarında bulunan vitaminleri ve antioksidan bileşikleri tanımlamak ve miktarlarını belirlemek amacıyla yapılmıştır. Bu bileşikler, Emilim, Dağılım, Metabolizma, Atılım ve Toksikolojik (ADMET) profilleri açısından analiz edildi. *T. molitor* larvalarının ekstraktlarının çeşitli gıda kaynaklı patojenlere karşı antibakteriyel ve antibiyofilm potansiyeli belirlenmiştir. Sonuçlar, vitaminler olarak yüksek miktarda vitamin B1 ve vitamin B2 ile antioksidan bileşikler olarak quercetin, luteolin ve apigenin bulunduğunu göstermiştir. Ekstraktlar, yüksek düzeyde antibiyofilm aktivitesi göstermiştir. Fonksiyonel gıda bileşenleri, gıda Ar-Ge sürecinde hesaplamalı analizlerle analiz edilebilir.

Anahtar Kelimeler
Tenebrio molitor, ADMET, LC-MS/MS, antibiyofilm.

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INTRODUCTION

Functional foods are defined as foods that provide an additional nutritional benefit, improve the quality of life and minimize the risk of disease [1]. Accordingly, research into the functionality of food formulations is increasing every day. Recently, edible insects have been emphasized as an alternative source of high protein, amino acid, high fat, carbohydrate, several vitamins, minerals and trace elements with digestibility [2]. Edible insects are part of the human diet for more than two billion people mainly in Africa, Asia, and Latin America [3,4]. Researchers have reported that fortifying foods with edible insects increases their nutritional value, increasing consumer acceptance and sustainability [5,6]. In this regard, the yellow mealworm is a species of particular interest due to its potential for high nutritional value (fatty acids, proteins, minerals, vitamins etc.) and relatively straightforward rearing [7-10]. The nutritional profile of *T. molitor* larvae powder has been reported to include 55.83% protein, 25.19% fat, 0.30% magnesium, 0.21% calcium, and 71.5 mg/100 g dry weight iron [11]. Dreassi et al. (2017) reported the total fat content of *T. molitor* larvae as 39.75-48.31% and 34.37-40.87% of its pupae form [7]. The mealworm larvae can be used in the human diet in a variety of forms, including whole, dried, ground, or powdered, as reported by the European Food Safety Authority (EFSA-Q-2018-00262) and approved by the European Council (July 2021) [12,13].

Recently, liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique has become a powerful analytical tool with advantages in terms of high sensitivity, selectivity and specificity [14]. LC-MS/MS allows the detection of food contaminants/residues or nutritional bioactive molecules [15-20]. There is increasing interest in the use of this technique in food quality control and food safety issues [21]. While other methods have several limitations in the extraction, purification and clean-up steps of polyphenols, LC-MS/MS has been reported to have fewer limitations in these processes [22].

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) analyses are widely used in drug research. However, the use of these analyses in the food industry may also be beneficial. Given the regular consumption of functional food components, it is important to predict the ADMET properties of these compounds and evaluate their positive effects on health. The determination of ADMET profiles of molecules has been simplified by computer-aided programmes compared to *in vitro* studies in terms of time, labour, equipment, etc. Natural products can also be analysed in this way, for example to determine the shelf life of food products for food safety or preservation purposes. These analyses can provide a scientific basis for the use of natural compounds in functional food applications and safety studies, offering time and cost advantages [23,24].

Vitamins play a fundamental role in nutrition, and research is ongoing to increase their potential for use as functional food ingredients and to ensure their standardization [25]. Antioxidants (carotenoids, polyphenols, phytosterols, tocopherols, tocotrienols, organo-sulphur compounds) are groups of compounds which neutralize free radicals and reactive oxygen species (ROS) in the cells [26]. There are several evidences supporting their involvement in numerous health promoting effects such as age-related conditions such as vascular injury, neurodegenerative disorders, cardiovascular oxidative stress and cancer [26-28]. Biofilm formation is one of the major problems in several areas such as food industry, and health care. The need of alternative methods for overcoming problem of biofilm formation has been emphasized in the literature [29]. The relation of ROS and the development of biofilms via promoting microbial attachment has been indicated in the literature. On the other hand, ROS can inhibit or kill microorganisms by inducing intracellular ROS production in the presence of a compound with oxidation-promoting activity [30]. Antioxidant molecules are reported to be less cytotoxic compared to antibiotics or other chemicals; therefore, they have been suggested as a potent alternative source for controlling biofilm-associated infections. Recently, research has revealed a new field of application for these compounds, demonstrating their capacity to influence biofilm formation in certain microbial pathogens such as *Staphylococcus aureus, Streptococcus mutans,* and *Pseudomonas aeruginosa* [27].

The aim of the study was to analyse the content of mealworm, to determine its structural and functional activities using a computer-based program, to investigate its functional usability in food products,

to determine antibacterial and antibiofilm effects of aqueous extracts of *T. molitor* larvae and to pave the way for further product development studies.

MATERIALS and METHODS

Rearing of Yellow Mealworm Larvae

T. molitor larvae were maintained under controlled laboratory conditions at 25 ± 1°C, 60 ± 5% relative humidity, and a 12:12 h light:dark photoperiod. Sterilized wheat bran was provided as the primary food source. Approximately 300 g of wheat bran (forming a ~5 cm substrate layer) was placed in each rearing container. The bran was renewed weekly and sieved when necessary to remove waste material and maintain hygiene. To supply moisture, fresh potato slices were provided. Potatoes were washed, peeled, and cut into slices approximately 3–5 mm thick and 2 × 2 cm in size. Ten grams of potato slices were added to each container and replaced every 48 h. Potato pieces were removed earlier if any signs of mold or spoilage were observed.

Pretreatment of Extracts

After weighing the insect powders, 4 mL of extraction solvent was added, and the extraction was performed by a vertical shaker (30 min, room temperature). Extracts were then obtained by centrifugation at 3600xg for 5 min and filtered through a PTFE filter. The extracts were kept at -80°C until chromatographic analysis. Through the pretreatment step, ultrapure water (18.2 MΩ.cm) was experimented.

Analysis of Compounds of *T. molitor* by LC-MS/MS Analysis

The contents of vitamins A, B and E, and antioxidant compounds of *T. molitor* were detected LC-MS/MS analysis by Altium International Laboratuvar Cihazları A.Ş. Experiments were performed in triplicate.

Analysis of compounds by LC-MS/MS were made on Agilent HPLC system (Agilent Technologies, Santa Clara, CA, USA) consisting of 1290 Flexible Pump, 1260 vial sampler and 1260 multicolumn thermostat coupled to Agilent 6465 triple quadrupole LC/MS (6465B, Agilent Technologies, Santa Clara, CA, USA) equipped with electrospray ionization (ESI) source. For determination of the concentrations of vitamins and antioxidants, Jasem LC-MS/MS and GC-MS analysis kits were used (Altium International Laboratuvar Cihazları. A.Ş., İstanbul, Türkiye). The analysis kits contained calibration standards, internal standard, mobile phases (mobile phase A and B), analytical column tailored for simultaneous analysis of the compounds, chromatographic and mass detection parameters. Calibrators and extracts were prepared due to the kit preparation protocols prior to injection to the LC-MS/MS and GC-MS systems. Compound quantification was made from calibration curves in accordance with the yield of the assigned IS. Agilent MassHunter Acquisition (version 10.1), Agilent MassHunter Qualitative Analysis (version 10.0) and Agilent MassHunter Quantitative Analysis (version 10.0) software programs were used for data acquisition, qualification and quantification.

Sample Preparation Protocol and Analysis Conditions of Vitamin A and Vitamin E Analysis Kit

To prepare calibrators and extracts, 50 µL of calibrator/extract was pipetted into a glass centrifuge tube and 25 µL of internal standard solution was added to the tube. 100 µL of Reagent-1 and 975 µL of Reagent-2 was added before vortexing the tube for 15 sec. The tube was centrifuged (3600xg, 5 min, room temperature) prior to decanting the supernatant into an amber HPLC vial. Chromatographic separation of the analytes was achieved utilizing kit analytical column and kit mobile phases on isocratic elution programme at a flow rate of 0.7 mL/min. The isocratic condition was 98% of mobile phase B for 6.0 min. The total running time was 6.0 min, and the sample injection volume was 10 µL. The temperatures of analytical column and autosampler were kept at 45°C and 8°C, respectively. Mass detections were conducted using mass spectrometer in positive polarity with MRM detection mode (Table 1). The mass spectrometer settings were as follows: drying gas temperature 350°C, drying gas flow 11 L/min, nebulizer pressure 50 psi, sheath gas temperature 400°C, sheath gas flow 11 L/min, capillary voltage 6000 V and nozzle voltage 1000 V.

Sample Preparation Protocol and Analysis Conditions of Vitamin B Forms Analysis Kit

To prepare calibrators and extracts, 100 µL of calibrator/extract was pipetted into a glass centrifuge tube and 25 µL of internal standard solution was added to the tube. Then, 700 µL of Reagent-1 was added before vortexing the tube for 5 sec. The tube was centrifuged (3600 x g, 5 min, room temperature) prior to decanting the supernatant into an amber HPLC vial. Chromatographic separation of vitamin B took place with kit analytical column implementing a solvent gradient program of

Table 1. MRM conditions of vitamins and antioxidant forms.

Compound Name	Precursor Ion (m/z)	Product Ion (m/z)	Fragmentor voltage (V)	Collision energy (eV)	Polarity
Vitamin A (Retinol)	269.2	93.1	50	24	Positive
Vitamin E (alpha-Tocopherol)	431.1	165.1	100	30	Positive
Vitamin B6 (Pyridoxal)	167.9	150	70	10	Positive
Vitamin B9 (Folic acid)	441.9	294.9	90	16	Positive
Vitamin B7 (Biotin)	245	226.9	90	13	Positive
Vitamin B3 (Nicotinamide)	122.9	79.9	90	22	Positive
Vitamin B1 (Thiamine)	265	121.9	70	16	Positive
Flavin adenine dinucleotide FAD	786	348.2	150	22	Positive
Riboflavin 5-monophosphate FMN	457	359	130	22	Positive
Vitamin B2 (Riboflavin)	377	242.7	130	25	Positive
4-OH-Benzoic acid	136.8	92.9	90	22	Negative
Apigenin	269.1	116.9	120	48	Negative
Caffeic acid	179	135	90	10	Negative
Chlorogenic Acid	353.1	190.9	90	6	Negative
Chrysin	253.1	119	140	30	Negative
Ferulic Acid	193	134	90	10	Negative
Galangin	269.1	211.1	90	30	Negative
Gallic Acid	169	125	90	8	Negative
Gentisic Acid	153	108	90	20	Negative
Kaempferol	285	145	120	40	Negative
Luteolin	285.1	132.9	150	40	Negative
Myricetin	317	150.8	130	28	Negative
Naringenin	271.1	119	100	20	Negative
p-Coumaric Acid	163	119.1	90	12	Negative
Protocatechuic aldehyde	137	108	90	20	Negative
Quercetin	301.1	150.9	90	18	Negative
Resveratrol	227	142.9	120	32	Negative
Rosmarinic Acid	359.1	133	100	40	Negative
Rutin	609.1	300	200	46	Negative
Salicylic Acid	137	93	80	10	Negative
Sinapic Acid	223.1	192.8	90	18	Negative
Trans-Cinnamic acid	147	102.8	90	8	Negative

mobile phase A and mobile phase B at a flow rate of 0.5 mL/min. The initial gradient of 0 %B was held for 1.5 min. The gradient was increased to 35 %B within 0.5 min. The gradient was increased to 90 %B within 1.5 min the gradient was 90 %B and maintained for 1.5 min. The gradient was returned to the initial condition in 5.0 min. The total running time was 10.0 min, and the sample injection volume was 10 µL. The temperatures of analytical column and autosampler were kept at 20°C and 8°C, respectively. Mass detections were conducted using mass spectrometer in positive polarity with MRM detection mode (Table 1). The mass spectrometer settings were as follows: drying gas temperature 150℃, drying gas flow 10 L/min, nebulizer pressure 40 psi, sheath gas temperature 400°C, sheath gas flow 10.

Sample Preparation Protocol and Analysis Conditions of Antioxidants Analysis Kit

To prepare calibrators and extracts, 50 µL of calibrator/extract was pipetted into a glass centrifuge tube and 20 µL of internal standard solution was added to the tube. 430 µL of Reagent-1 was added before swirling the tube

for 5 sec. The tube was centrifuged (3600xg, 5 min, room temperature) before decanting the supernatant into an HPLC vial. Chromatographic separation of the antioxidants was accomplished using kit analytical column and gradient elution programme. During the injections, the gradient conditions were as follows: 0–1.5 min maintained at 2%B, 1.5–4.5 min increased to 75%B, 4.5–7.5 min increased to 95%B, and 7.5–13.0 min returned to 2%B for re-equilibration. The analysis was performed in a total run time of 13.0 min. The temperatures of analytical column and autosampler were kept at 25 and 8°C, respectively. The injection volume was set as 10 µL. Mass detections was acquired in negative ion MRM mode. The mass spectrometer settings were as follows: drying gas temperature 350℃, drying gas flow 10 L/min, nebulizer pressure 50 psi, sheath gas temperature 400℃, sheath gas flow 10 L/min, capillary voltage 4000 V and nozzle voltage 500 V (Table 1).

Computational Analysis of Vitamins and Antioxidant Compounds of *T. molitor*

The vitamins A, B and E, and antioxidant compounds of *T. molitor* identified by LC-MS/MS were analysed for physicochemical, medicinal chemistry, absorption-excretion and toxicity properties by Admetlab 3.0 (https://admetmesh.scbdd.com) [21]. The two-dimensional structures and canonical SMILES of the compounds were taken from the PubChem Compound (https://pubchem.ncbi.nlm.nih.gov).

Antibacterial and Antibiofilm Test of *T. molitor* Larvae Extracts

6 g of *T. molitor* larvae were weighed and dissolved in 120 mL of water to prepare an aqueous extract. Dry extracts were then obtained and prepared at a concentration of 2.3 mg/mL in the first well of microplate assays. Serial dilutions were carried out. The concentrations tested were 2.3 mg/mL, 1.1 mg/mL, 0.6 mg/mL, 0.3 mg/mL, 0.15 mg/mL and 0.075 mg/mL.

Antibacterial effect of the extract of *T. molitor* was tested against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* O157:H7, *Clostridium perfringens*, *Salmonella* sp., *Listeria monocytogenes* which were isolated from food samples by Eurofins Scientific Food Analysis Laboratory. The antibacterial tests were performed by Tryptic Soy Broth (TSB) and in 96-well microplates. The optical density (OD) of bacterial cultures was adjusted to 0.02 at 600 nm in a 96-well plate. The extract sample was tested for 2.3 mg/mL to 0.075 mg/mL dilutions by serial dilution.

T. molitor larvae extract was also tested for antibiofilm effect. TSB was added to each well in 96-well microplates and six serial dilutions of the extract were made. The incubated microplates (37°C, 24 h, without agitation) were washed with physiological saline and dried (60°C). The biofilm staining procedure included adding 200 µL of 0.1% crystal violet, keeping at room temperature for 10 min, wahing three times and drying. A microplate reader was used to read the absorbance at OD 590 nm after 200 µL of ethanol was added to the wells. The experiments were carried out in triplicate.

Statistical Analysis

All experiments were carried out in triplicate and data were expressed as mean ± standard deviation (SD). Statistical differences among groups were analyzed using one-way ANOVA followed by Tukey's post-hoc test. Statistical significance was accepted at $p < 0.05$.

RESULTS AND DISCUSSION

LC-MS/MS Analysis

In the present study, a total of 10 vitamins, and 23 antioxidant compounds, were analyzed by LC-MS/MS in *T. molitor* larvae samples. The amount of vitamin A, vitamin B, and vitamin E content were determined by LC-MS/MS. Vitamin B1 has been reported to play an important role in blood circulation, carbohydrate metabolism, and brain function. The role of the vitamin B2 in the digestion and metabolism of proteins, fats, and carbohydrates has also been suggested [32]. According to our results, vitamin B1 and vitamin B2 were the most abundant ones. Vitamin A and vitamin E were found to be present at much lower levels than the other vitamins (Table 2).

A total of 23 antioxidant compounds were also analyzed by LC-MS/MS analysis (Table 3). Among ten compounds detected in the aqueous extract of *T. molitor* larvae, the most abundant antioxidant compounds were gentisic acid (17.08%), protocatechuic acid (44.33%), and protocatechualdehyde (22.25%). Martínez-Pineda et al. (2024) reported that, of nine detected phenolic compounds, including malvidin, chlorogenic acid, apigenin, epicatechin, naringenin, quercetin, gallic acid, ferulic acid and coumaric acid, apigenin was present in high quantities in defatted *T. molitor* larvae [33]. They

Table 2. The vitamin content of *T. molitor* larvae samples (mg/L).

	Vitamins	Aqueous Extract
Vitamin B	Vitamin B6 (Pyridoxal)	9.253
	Vitamin B9 (Folic acid)	2.023
	Vitamin B7 (Biotin)	7.995
	Vitamin B3 (Nicotinamide)	0.849
	Vitamin B1 (Thiamine)	36.650
	Flavin adenin dinucleotide FAD	11.303
	Riboflavin 5-monophosphate FMN	2.446
	Vitamin B2 (Riboflavin)	60.433
	Vitamin A	0.034
	Vitamin E	0.005

Table 3. The antioxidant content of *T. molitor* (µg/L).

Compounds	Aqueous Extract
Gallic Acid	n.d.
Gentisic Acid	133.581
Protocatechuic Acid	354.626
Protocatechualdehyde	174.078
4-OH-Benzoic acid	n.d.
Salicylic Acid	n.d.
Chlorogenic Acid	n.d.
Caffeic acid	n.d.
p-Coumaric Acid	n.d.
Ferulic Acid	61.087
Rosmarinic Acid	11.651
Sinapic Acid	n.d.
Trans-Cinnamic acid	n.d.
Rutin	n.d.
Resveratrol	4.391
Myricetin	n.d.
Naringenin	n.d.
Quercetin	2.549
Luteolin	16.730
Kaempferol	22.846
Apigenin	0.749
Galangin	n.d.
Chrysin	n.d.

*n.d.: not determined

utilized a mechanical cold pressing method following blanching and hot-air dehydration (75°C, 6 h) that could cause differences in phenolic recovery. Solvent extraction systems are known to increase the recovery of lipophilic compounds such as phenolic compounds. However, since mechanical pressing occurs due to matrix disruption, the yield of bioactive compounds may be lower. In summary, the use of different substrates or extraction methods (e.g. solvent selection or temperature) may cause variations in the levels of phenolic and flavonoid compounds.

Solvents such as aqueous and ethanol are preferred because they are GRAS. Furthermore, testing the aqueous extract is more advantageous for its potential use in the food industry. From this point of view, we tested aqueous extracts of T. molitor larvae. Extraction methods may also influence the compounds present in source material. For example, Caldas et al. (2018) studied the phenolic compounds from grape skin using conventional extraction by mechanical agitation and non-conventional extraction (ultrasound-assisted extraction and microwave-assisted extraction) methods [34]. They reported that ultrasound-assisted and microwave-assisted extractions provided higher phenolic compounds as compared to conventional extraction. On the other hand, temperature is also an important factor in the extraction yield. It has been reported that higher temperatures increase the release of larger amounts of phenolic compounds. However, the temperature must be under control due to the thermal instability of the compounds. An example of such a study was conducted by Erşan and colleagues (2018). They reported that increasing the extraction temperature from 110 to 150°C increased the phenolic yield from pistachio hulls, while increasing the temperature from 170 to 190°C resulted in a significant decrease in phenolic yield [35].

Computational Analysis

ADMET Properties of Vitamins

A comprehensive assessment of the ADMET properties of the 10 vitamins was conducted. Vitamin B1 and vitamin B2 were found to be more abundant compared to other vitamins in the aqueous extracts of *T. molitor* larvae. These molecules were characterised by their low molecular weight, with a molecular weight of less than 500 Da, and their solubility in aqueous solutions. vitamin B1 was found to have greater lipophilicity and was identified as a particularly attractive vitamin. Furthermore, it was established that these vitamins were colloidal aggregator and reactive, promiscuous compounds. They were found to be absorbed by human intestial system. The bioavailability of F50% in vitamin B2 was found to be high. The half-life was found to be intermediate. The more lipophilic and colloidal

aggregator properties of vitamin B1 support its use in oil-based systems, while its reactive and promiscuous character suggests that it is biologically versatile but sensitive in terms of oxidative stability. The high oral bioavailability of riboflavin B2 and the moderate half-life of both vitamins suggest that they may be effective with regular consumption and should be considered as functional food ingredients. The GASA score was found to be inadequate for riboflavin, while the levels of vitamin B1 were found to be excellent and easily attainable (Table 4).

Vitamin B1 was classified as excellent for DILI. The safety of vitamin B2 has been demostrated for use in the context of allergic contact dermatitis. Vitamin B2 was identified as non-carcinogens. Vitamin B1 was found to be non-hepatoxic. The drug-induced nephrotoxicity values were found to be within an acceptable range or non-nephrotoxic for the compounds. They were found to be non-Hek293 cytotoxic or medium level Hek293 cytotoxic. These vitamins were identified as ARE active. Vitamin B2 has been detected to be safe for skin irritation. These molecules were biodegradable (Table 5). Both vitamins were found to be generally safe from a toxicological point of view and classified as environmentally biodegradable.

Based on the prediction of the lipophilic properties of food molecules through these analyses, it may demonstrate the ability to assess whether they negatively affect the processes of spreading into the biofilm matrix, interacting with the cell membrane, and adhesion. For example, it can be predicted that Vitamin A (LogP 3.859) and Vitamin E (LogP 5.663) in particular may interact with the biofilm matrix and disrupt its stability.

As diffusion is expected to be low within the biofilm structure, it can be hypothesised that low-molecular-weight molecules may diffuse more easily. Therefore, vitamins B3 (122 Da) and B6 (167 Da) are predicted to diffuse more easily into the biofilm structure. High PAMPA and HIA values are indicative of the diffusion of molecules into cells. From this perspective, molecules with high PAMPA and HIA values may inhibit the quorum sensing mechanism, which is important in biofilm processes, or exert an inhibitory effect on metabolic pathways. Compounds predicted to be permeable may interact more readily with lipid membranes or penetrate the hydrophobic regions of the biofilm matrix. Conversely, compounds predicted to be poorly permeable may have limited ability to diffuse through bacterial membranes or dense extracellular polymeric substances (EPS).

Table 4. The ADME (Physicochemical Property, Medicinal Chemistry, Absorption and Excretion) properties of vitamins of *T. molitor* larvae.

Vitamins	Molecular Weight	LogS	LogP	QED	GASA	NPscore	Colloidal aggregators	Reactive compunds	Promiscuous compunds	PAMPA	HIA	F50%	T1/2
Vitamin B6 (Pyridoxal)	167.06	-1.212	0.261	0.625	Easy	0.701	0.116	0.191	0.217	++	- -	-	1.691
Vitamin B9 (Folic acid)	441.14	-5.166	-2.367	0.259	Easy	-0.28	0.02	0.023	0.037	+++	- - -	- - -	2.089
Vitamin B7 (Biotin)	318.1	-4.148	2.801	0.455	Easy	-1.447	0.027	0.06	0.001	- - -	- - -	++	0.446
Vitamin B3 (Nicotinamide)	122.05	0.252	-0.377	0.577	Easy	-1.299	0.006	0.464	0.015	++	- - -	- - -	2.083
Vitamin B1 (Thiamine)	265.11	-1.71	-0.228	0.794	Easy	-0.1	0.106	0.018	0.033	+++	++	+++	1.161
Flavin adenin dinucleotide FAD	785.16	-3.026	-2.654	0.44	Hard	0.719	0.046	0.233	0.02	+++	- - -	- - -	2.044
Riboflavin 5-monophosphate FMN	455.1	-2.936	-1.123	0.19	Hard	0.08	0.154	0.018	0.011	+++	- - -	- - -	1.795
Vitamin B2 (Riboflavin)	376.14	-3.053	-1.377	0.328	Hard	0.065	0.195	0.017	0.034	+++	- - -	- -	1.801
Vitamin A	286.23	-4.054	3.859	0.661	Easy	2.615	0.403	0.92	0.222	- -	- - -	-	0.262
Vitamin E	430.38	-7.622	5.663	0.359	Easy	1.5	0.933	0.519	0.028	- - -	- - -	+++	0.28

"+++" (0.9–1.0), "++" (0.7–0.9), "+" (0.5–0.7), "–" (0.3–0.5), "– –" (0.1–0.3), and "– – –" (0–0.1) represent the probability score ranges predicted by the ADMET model.

Table 5. The ADME (Toxicity) properties of vitamins of *T. molitor* larvae.

Vitamins	DILI	FDAMDD	Skin Sensitization	Carcinogenicity	Human Hepatotoxicity	Drug-induced Nephrotoxicity	Hek293 Cytotoxicity	BCF	SR-ARE	Skin Sensitization Rule	Non-Biodegradable
Vitamin B6 (Pyridoxal)	0.144	0.207	0.798	0.573	0.379	0.167	0.088	0.327	- - -	2	1
Vitamin B9 (Folic acid)	1.0	0.615	0.018	0.513	0.959	0.98	0.136	-0.05	- - -	3	0
Vitamin B7 (Biotin)	0.6	0.24	0.924	0.195	0.156	0.255	0.168	1.03	-	1	2
Vitamin B3 (Nicotinamide)	0.607	0.119	0.628	0.634	0.518	0.184	0.047	0.046	- - -	0	1
Vitamin B1 (Thiamine)	0.014	0.874	1.0	0.85	0.105	0.176	0.314	0.532	- - -	2	0
Flavin adenin dinucleotide FAD	1.0	1.0	0.1	0.449	0.166	0.997	0.636	0.042	- - -	2	1
Riboflavin 5-monophosphate FMN	0.934	0.986	0.03	0.515	0.988	0.999	0.011	0.054	- - -	0	0
Vitamin B2 (Riboflavin)	0.35	0.44	0.001	0.186	0.575	0.639	0.143	-0.035	- - -	0	0
Vitamin A	0.526	0.651	0.922	0.666	0.796	0.661	0.276	2.486	+++	1	0
Vitamin E	0.007	0.317	0.991	0.404	0.632	0.058	0.098	2.101	- -	2	0

"+++" (0.9–1.0), "++" (0.7–0.9), "+" (0.5–0.7), "–" (0.3–0.5), "– –" (0.1–0.3), and "– – –" (0–0.1) represent the probability score ranges predicted by the ADMET model.

In terms of functional foods, considering the values, the fact that the half-life values are not very high suggests that the consumption of bioactive compounds ingested through food may be safe without excessive accumulation or toxicity.

ADMET Properties of Antioxidants

A comprehensive assessment of the ADMET properties of 10 antioxidants was conducted. Gentisic acid, protocatechuic acid and protocatechualdehyde were more abundant in the aqueous extracts of *T. molitor* larvae when compared to the remaining compounds according to LC-MS/MS analysis.

These molecules were less than 500 Da, soluble and lipophilic. The QED were poor for these molecules. GASA was found to exhibit an excellent and easily accessible level. NP scores demonstrated that the compounds are ideal candidates, and they were found to comply with Lipinski's rule. Therefore, they can be well absorbed orally and may be effective in functional food formulations. They were identified as excellent colloidal aggregators, poor reactive and poor promiscuous compounds. The PAMPA values of tested compounds were classified as moderately or poor values. They were rated as highly efficacious with regard to HIA. Except for gentisic acid, protocatechuic acid and protocatechualdehyde had low F50% values, while their T1/2 values ranged from 1,729 to 2.257 (Table 6).

Protocatechualdehyde has been found to exhibit excellent DILI properties and negative DILI effects. The following compounds have been defined as having excellent FDAMDD properties, i.e. low toxicity potential: gentisic acid and protocatechuic acid. The safety of gentisic acid for use in the context of allergic contact dermatitis has been determined to be moderate, while the sensitisation of other compounds was classified as poor. It was determined that gentisic acid was identified as non-carcinogens. They were analysed were moderately or excellent hepatotoxic. In addition, the drug-induced nephrotoxicity values of analysed compounds were found to be within an acceptable range or non-nephrotoxic for the compounds. Gentisic acid, protocatechuic acid, and protocatechualdehyde were found to be non-Hek293 cytotoxic. Protocatechualdehyde was ARE active. They were found to cause skin irritation but were non-biodegradable (Table 7). The high HIA values but low

F50% values indicate the need for supportive systems (emulsion, nanocarrier, etc.) for systemic effects. It was found to be generally safe in toxicological analyses, but limiting aspects such as skin irritation and non-biodegradability should be carefully evaluated.

Of the antioxidants tested, gentisic acid, protocatechuic acid, ferulic acid and rosmarinic acid appear to be able to penetrate the biofilm matrix more effectively through passive membrane transport. This suggests that these compounds may be responsible for the antibiofilm activity.

The fact that phenolic antioxidant compounds comply with Lipinski's rule and have positive PAMPA values suggests that they can interact with membranes. Their predicted moderate half-life values suggest that excessive accumulation will not occur. The predicted low reactivity and low level of cytotoxicity may explain the mechanisms underlying antibiofilm activity.

For example, gentisic acid and protocatechuic acid estimated having low molecular weight (~154 Da) and moderate lipophilicity. Their high PAMPA values suggests good passive membrane interaction potential. This may indicate that they could play a role in the antibiofilm effect via diffusion into EPS matrix or interaction with cell surface.

Antibacterial and Antibiofilm Effect of *T. molitor* Larvae Samples Against Foodborne Pathogens

We evaluated the antibacterial effect of *T. molitor* extract against *S. aureus*, *B. cereus*, *E. coli* O157:H7, *C. perfringens*, *Salmonella* sp., *L. monocytogenes* which were isolated from food samples. Antibacterial activity was observed only against *S. aureus* and *C. perfringens*. However, as these observed effects were less than 50%. The inhibitory percentage of *T. molitor* extract (28.11%) on the growth of *S. aureus* was considered to be almost ineffective. A very low inhibitory effect on the growth of *C. perfringens* was only observed at concentrations of 0.3 mg/mL and 0.15 mg/mL with the inhibition percentages of 36.1% and 30.9% respectively. No significant antibacterial activity was observed against other tested bacteria. Hwang et al. (2022) reported the potential natural preservative effect of *T. molitor* larvae against *E. coli*, *B. cereus* and *S. aureus* [36]. Shin et al. (2019) showed antibacterial effect of chitosan from mealworm larvae against *E. coli*, *B. cereus*, *L. monocytogenes* and *S. aureus* [37]. However, we did not detect any antibacterial effect against these bacteria except *S. aureus*. Differences can be observed depending on the type of bacteria, the concentration used and the method used. The observed differences may be directly associated with the methodological design of the present study, particularly the use of a crude aqueous extract without organic solvent extraction or fractionation, which may have resulted in

Table 6. The ADME (Physicochemical Property, Medicinal Chemistry, Absorption and Excretion) properties of antioxidants of *T. molitor* larvae samples.

Compounds	Molecular Weight	LogS	LogP	QED	GASA	NPscore	Colloidal aggregators	Reactive compunds	Promiscuous compunds	PAMPA	HIA	F50%	T1/2
Gentisic Acid	154.03	-2.037	1.392	0.522	Easy	0.739	0.074	0.999	0.861	+++	---	--	1.729
Protocatechuic Acid	154.03	-1.697	1.001	0.522	Easy	0.739	0.192	0.999	0.811	+++	--	++	2.257
Protocatechualdehyde	138.03	-1.269	1.123	0.448	Easy	1.104	0.414	1.0	0.593	+	--	+++	2.046
Ferulic Acid	194.06	-1.974	1.484	0.715	Easy	0.926	0.21	0.993	0.866	+++	-	+++	1.876
Rosmarinic Acid	360.08	-2.795	1.8879	0.298	Easy	1.128	0.903	0.663	0.533	+++	---	+++	1.965
Resveratrol	228.08	-3.352	2.798	0.692	Easy	0.754	0.679	0.992	0.845	-	---	+++	1.536
Quercetin	302.04	-3.722	1.448	0.434	Easy	1.701	0.891	0.698	0.921	+	--	+++	1.586
Luteolin	286.05	-4.017	2.247	0.511	Easy	1.499	0.867	0.707	0.897	-	---	+++	1.373
Kaempferol	286.05	-3.648	1.965	0.546	Easy	1.546	0.842	0.728	0.928	++	---	+++	1.388
Apigenin	270.05	-4.126	2.981	0.632	Easy	1.358	0.729	0.782	0.9	+	---	+++	1.203

"+++" (0.9–1.0), "++" (0.7–0.9), "+" (0.5–0.7), "–" (0.3–0.5), "– –" (0.1–0.3), and "– – –" (0–0.1) represent the probability score ranges predicted by the ADMET model.

Table 7. The ADME (Toxicity) properties of antioxidants of *T. molitor* larvae samples.

Antioxidants	DILI	FDAMDD	Skin Sensitization	Carcinogenicity	Human Hepatotoxicity	Drug-induced Nephrotoxicity	Hek293 Cytotoxicity	BCF	SR-ARE	Skin Sensitization Rule	Non-Biodegradable
Gentisic Acid	0.345	0.193	0.64	0.3	0.434	0.363	0.082	0.186	+++	4	1
Protocatechuic Acid	0.573	0.175	0.906	0.334	0.396	0.13	0.032	0.298	+	5	1
Protocatechualdehyde	0.261	0.469	0.993	0.571	0.254	0.011	0.228	0.715	- -	7	1
Ferulic Acid	0.308	0.112	0.897	0.307	0.483	0.524	0.038	0.203	-	6	0
Rosmarinic Acid	0.595	0.597	1.0	0.084	0.367	0.11	0.207	0.902	- -	8	1
Resveratrol	0.011	0.688	1.0	0.263	0.841	0.307	0.809	1.14	+++	5	1
Myricetin	0.839	0.864	0.996	0.502	0.325	0.003	0.489	0.98	++	8	1
Naringenin	0.334	0.773	0.708	0.656	0.659	0.274	0.868	1.304	++	6	1
Kaempferol	0.703	0.805	0.621	0.716	0.386	0.019	0.763	1.242	+++	4	1
Apigenin	0.743	0.882	0.645	0.793	0.435	0.021	0.855	1.308	+++	3	1

"+++" (0.9–1.0), "++" (0.7–0.9), "+" (0.5–0.7), "–" (0.3–0.5), "– –" (0.1–0.3), and "– – –" (0–0.1) represent the probability score ranges predicted by the ADMET model.

lower concentrations of active antibacterial compounds. Additionally, the tested concentration range (0.075–2.3 mg/mL) may have limited the detection of stronger antibacterial effects.

To the best of our knowledge, there is no study that has evaluated the antibiofilm effect of *T. molitor.* The antibiofilm activity of *T. molitor* extract against *S. aureus* was recorded at the concentration of 2.3 mg/mL with the inhibition ratio of 74.55%. At lower concentrations, antibiofilm activity was less than 50%. The inhibition percentages on the biofilm formation of *S. aureus* were recorded as 44.99, 33.62, 20.83, 13.86 and 12.38 at the concentrations of 1.1 mg/mL, 0.6 mg/mL, 0.3 mg/mL, 0.15 mg/mL and 0.075 mg/mL, respectively. The biofilm structure of *E. coli* O157:H7 was inhibited by percentages ranging from 52.84 to 96.08. *T. molitor* sample had a high biofilm inhibitory effect on *B. cereus* with the percentages of 86.00, 81.75 and 61.01 at the concentrations of 2.3 mg/mL, 1.1 mg/mL and 0.6 mg/mL, respectively. Significant antibiofilm activity was observed against *C. perfringens* independent of the concentration, except the concentration of 0.075 mg/mL. The inhibition ratios were recorded as 83.91%, 85.03%, 77.75%, 66.54% and 71.16% at the cocentrations of 2.3 mg/mL, 1.1 mg/mL, 0.6 mg/mL, 0.3 mg/mL and 0.15 mg/mL. The antibiofilm effect against *Salmonella* sp. was determined at the varying percentages between 36.11 and 74.82 and the concentrations of 0.15 mg/mL and 0.075 mg/mL were found to have the most successful ones. The only concentration with antibiofilm activity on *L. monocytogenes* was 0.075 mg/mL with an inhibition rate of 45.59% (Figure 1).

Biofilm formation is one of the major problems in several areas such as food industry, and health care. The need of alternative methods for overcoming problem of biofilm formation has been emphasized in the literature [29]. From this point of view, our results are promising for having potential antibiofilm effect.

The pronounced antibiofilm activity observed despite weak antibacterial effect suggests a mechanism independent of direct bactericidal action. One of the underlying mechanisms may involve interference with quorum sensing system. The quorum sensing (QS) system is a form of bacterial communication regulated by high population density via gene expression, resulting from intraspecies, interspecies or interkingdom interactions [38,39]. Small molecules are used by bacteria to communicate with one another [40].

Several natural bioactive compounds are reported to have potential ability to attenuate biofilm formation by downregulating QS-regulated genes with no effect on planktonic cell viability [41].

There are numerous studies on this subject in the literature. For example, Matsunaga et al. (2010) reported that some species of catechins inhibited autoinducer 2-regulated QS system and inhibited biofilm formation by Eikenella corrodens [42]. Naga et al. (2023) demonstrated that methyl gallate from

Mangifera indica reduced the expression of QS-regulatory genes in Pseudomonas aeruginosa [43]. The compound of Juglone obtained from Juglans nigra was reported to suppress the pathogenicity of P. aeruginosa, and PQS-controlled virulence factors such as pyocyanin and motility [44].

Additionally, certain metabolites may interfere with extracellular polymeric substance (EPS) via weakening biofilm integrity. Disruption of EPS production or degradation of matrix components has been reported as an effective antibiofilm strategy for various natural compounds. For example, carvacrol biofilm formation and EPS synthesis of Pectobacterium carotovorum [45]. Overall, the reasons for the antibiofilm activity being over 85% against B. cereus, E. coli O157:H7 and C. perfringens may include QS inhibition and disruption of EPS production or degradation of matrix components, but detailed research is required.

CONCLUSION

The analysis of *T. molitor* revealed higher levels of bioactive compounds in the aqueous solvent. LC-MS MS showed that *T. molitor* larvae have a higher abundance vitamin B1 and vitamin B2, antioxidant compounds (quercetin, luteolin, and apigenin). The feeding substrate is considered important for the nutritional profile of the compounds. Overall, mealworms can be used in various products such as energy bars, protein powders, flours and other functional foods with a valuable nutritional profile taking into account consumer acceptance trends. ADMET profiling can be also useful in the food sector. Determining functional food ingredients to develop safe and healthy foods, predict the metabolism of food ingredients, assess the safety of food ingredients, evaluate the potential toxicity of food additives, improve bioavailability, and predict potential interactions is a very rapid option. Rapid assessment of new ingredients

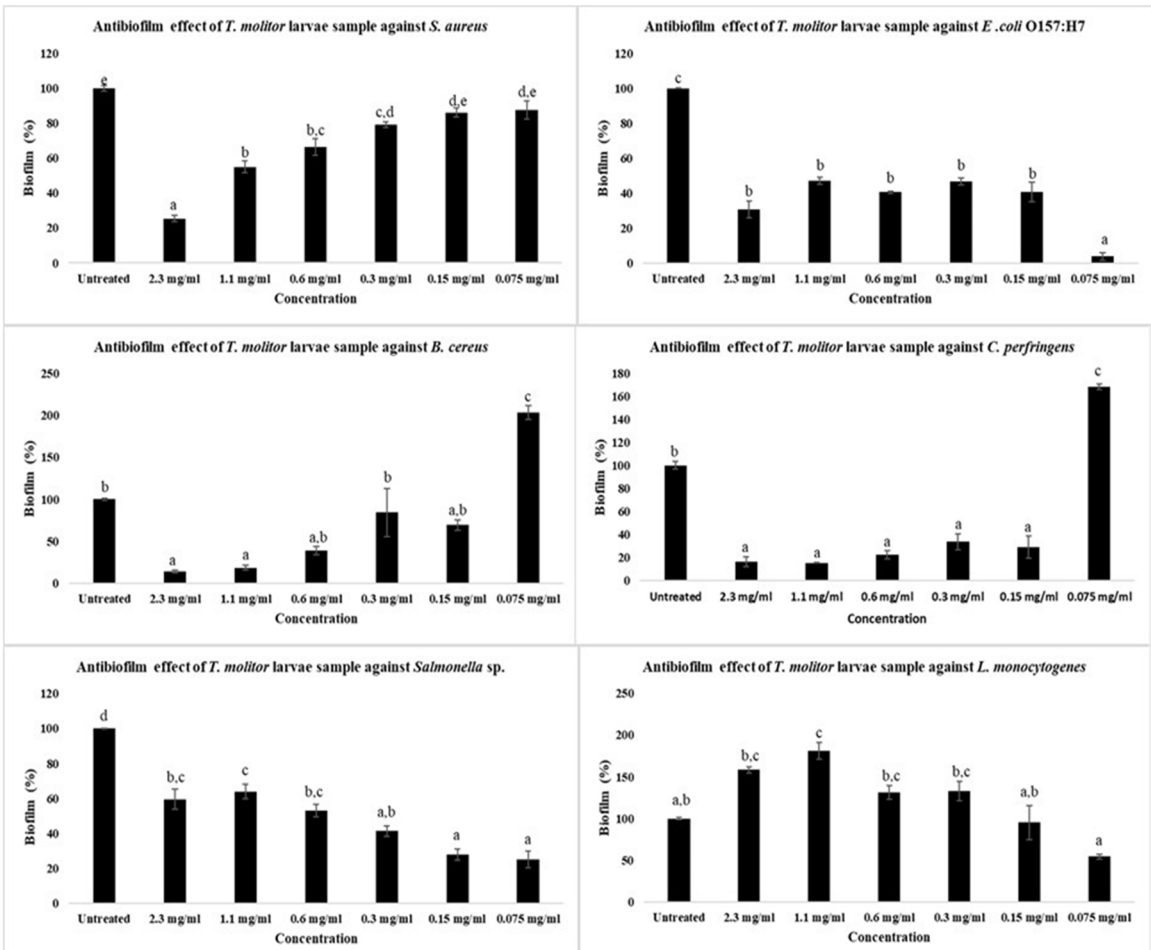


Figure 1. Antibiofilm effect of *T. molitor* larvae samples against foodborne pathogens.

can save time, effort and cost in the innovation process. The *in vitro* experiments showed low antibacterial activity only against *S. aureus* and *C. perfringens*, but promising results for antibiofilm activity. The extracts showed the lowest efficacy against *L. monocytogenes* but above 70% against the other bacteria tested. Antibiofilm activity was over 85% against *B. cereus, E. coli* O157:H7 and *C. perfringens*. This suggests that *T. molitor* peptides, proteins or other compounds could be used as effective agents in food industry.

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