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Foodomics-based metabolites profiling of the Greek yogurt incorporated with unripened papaya peel powder

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ABSTRACT

The food waste of the fruit processing industry is rich in many bio-active components such as polysaccharides, polyphenols, peptides, etc. that own multifaceted health benefits. The valorization of this waste is an intriguing optimization method for various dairy products. Meanwhile, LC-MS-based foodomics has been an emerging approach for the quantitative and qualitative analysis of dairy foods. Untargeted metabolomics has been done of the optimized functional yogurt that contains different levels of unripened papaya peel powder (UPPP) using high-resolution mass spectroscopy for analysis of added bio-active components in the matrix. UPPP comprises a high content of phytochemicals which could give functionality and therapeutic effect to the Greek yogurt. A total of 36 functional metabolites have been identified which have various health-beneficial attributes. Kaempferol, ostruthin, putative carpaine derivatives, etc. are some of the metabolites of high importance with a wide area coverage in the metabolome. This work highlights the bioactivity of the UPPP and its prebiotic properties added to the functional yogurt as an independent ingredient. The incorporated plant-based ingredients like UPPP can effectively enhance the functional attributes of Greek yogurt, which is a potential synbiotic food.

1. Introduction

Foodomics has been an intriguing method for the evaluation of food quality, and traceability which is reliable, effective, sensitive, and economical (Afzaal et al., 2022). Numerous omics analytical platforms are being used to study the comprehensive and in-depth metabolomes of various food products due to the complexity and dynamic nature of the metabolites. The most frequently used tools are Fourier transform infrared (FT-IR) spectroscopy, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, etc. These technologies elucidate an insight and structured examination method with possibilities for uncovering the process of action of bioactive elements, dietary intervention, and finding novel biological markers. The application of metabolomics tools also ameliorates the analysis of metabolite variations throughout the processing of foods, enabling improved efficiency of processing techniques and the development of products with enhanced quality (Utpott et al., 2022).

Yogurt is an end product of the lactic acid fermentative microflora of the milk with the inclusion of a starter culture comprising *Lactobacillus delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus* (Kok & Hutkins, 2018). Generally, yogurt contains around 3.5 % fat, 8.5 % solids-not-fat, 0 %–10 % sugar, and 0.0–2 % stabilizer. It is recommended that it be devoid of any foreign materials found in milk, such as mineral oil, vegetable fat, and animal fat. Yogurt shows homology with the curd, and in India, it is very popular by the name of "*Dahi*". Along with a source of probiotics and an alternative for lactose intolerance patients, this dairy product has its role in curating several physiological discomforts such as diarrhea, obesity, irritable bowel syndrome (IBS), etc. Adding fruit processing waste to the yogurt matrix that is abundant in bioactive chemicals, dietary fibers, and affordable sources of antioxidants could lead to a formulation of functional dairy products (Soleimanian et al., 2022).

The Food and Agriculture Organization of the United Nations projects that global papaya (*Carica papaya* L.) production will increase by 2.1 % yearly, reaching 16.6 million tonnes in 2029 (Rodrigues et al., 2021). Annually, large amounts of papaya are produced for a variety of

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reasons, which results in the production of a sizable quantity of peels as a waste product. Papaya peels have excessive dietary fiber (constituted with soluble and insoluble portions), and an ample number of phytochemicals (Angulo-López et al., 2022). Nutritionally, incorporating unripe papaya peel powder (UPPP) in dairy foods is preferable for health promotion because of the high level of fiber and bioactive in the peel, which elucidates different therapeutic effects. Food products containing dietary fiber have been demonstrated to provide many health advantages such as lessening the risk of heart disease, preventing cancers, and gastrointestinal problems, lowering blood cholesterol, and aiding in weight management (Soliman, 2019).

Fermented dairy products have been reported to support the immune system and their consumption is associated with reduced risk of several diseases at the population level due to their probiotic bacterial component (Ahmed et al., 2021). Additionally, research has been conducted on fortifying yogurts with plant ingredients (Reeta et al., 2018; Sarker et al., 2023) to promote the growth of probiotics and improve the health benefits of yogurts. According to emerging research, obesity and general health may be influenced by gut microbiota, and a plant-based diet is thought to encourage a diversified and healthy gut microbiota (Sidhu et al., 2023). Yogurt and a plant-based diet together may thereby improve the quantity and variety of intestinal flora as well as provide many bioactive compounds.

In the present investigation, we have examined the total added bioactive metabolites in the functional yogurt developed by the addition of green papaya peel powder which yields a symbiotic dairy product inculcating the attributes of both, i.e., probiotics and prebiotics. The high-resolution accurate mass spectrometer was used for the detailed profiling of the optimized Greek yogurt for the characterization of the differential and highly expressed metabolites.

2. Materials and methods

2.1. Materials and reagents

In this study, the organic solvents and reagents were procured from Sigma-Aldrich (Bangaluru, India). Other materials, such as disposable syringes with syringe filters (25 mm, 0.22 μm PVDF), 2 mL chromatography amber vials, and glass beakers, were obtained from Hi Media (Mumbai, India). Polypropylene falcon tubes (50 mL) were acquired from Fisher Scientific (Bangaluru, India).

The unripened papaya fruits were obtained from the Horticultural unit of the Banaras Hindu University. Peels were separated from the whole fruit using a stainless-steel knife and were rinsed twice with water to remove any adhering mucilage and then cut into pieces (Size: 2 x 2 cm^2; thickness: 3.45 mm). They were distributed uniformly on a clean tray and dried using the tray drier at the thermal range of 45-65° C for 48 h to obtain UPPP in three replications.

2.2. Development of yogurt

Batch culture (*S. thermophilus* and *L. bulgaricus*, grown separately first and then mixed in the ratio of 1:1) of the yogurt (100 g) was procured from the National Dairy Research Institute, Karnal, stored at 5° C, and added to the pasteurized milk at the rate of 2 %. A total of seven set-type yogurt treatments were prepared as per the method given by Ahmed et al. (2021) with slight modifications, the experiment was independently repeated three times for each formulation. The treated formulations were as follows: T^1: milk + 1.5 g UPPP, T^2: milk + 2 g UPPP, T^3: milk + 3 g UPPP, T^4: milk + 6 g UPPP, T^5: milk + 8 g UPPP, T^6: milk + 10 g UPPP, and T^7: milk only (control sample). The maximum concentration of the peel powder in yogurt was maintained at a level of 10 % so that the fermentation process was not affected. The coagulation of yogurt was broken (pH ~ 4.8) by stirring until the peel powder was uniformly incorporated followed by storage under refrigerated conditions at 5° C until analysis (Reeta et al., 2018). After the triplicates sensorial analysis and rheological studies using a texture profile analyzer (Model: CT3, Brookfield, Mumbai, India) of the independent samples, the sample having 3 g of UPPP (T^3) was found acceptable among all.

2.3. Metabolomics analysis of yoghurt

The three technical replicates of the optimized frozen yogurt (T^3) samples (100 mg) were added with 300 μL (methanol: acetonitrile; 1:1) solvent, and homogenization was done with zirconia beads in a shaker for 20 min. Subsequently, the homogenates undergo a centrifugation process at 3500 rpm for 10 min. The hydrophobic component was eliminated from the supernatant by filtering it through a 0.22 mm diameter syringe filter, and 2 mL of the extract was applied in the LC–orbitrap–MS analysis. An Ultimate 3000 RSLC (Thermo Fisher Scientific) combined with a Q Exactive Mass Spectrometer with an electrospray source functioning in positive-ion mode constituted up the LC-MS system. According to Hiraga et al. (2021), the capillary temperature was 300 °C and the spray voltage was 3.2 kV. The high-resolution mass spectrometer instrument was run in single survey scan mode (scan range: *m/z* 80–1200; resolution: 70 000 at *m/z* 200) and full scan MS and collision-induced dissociation (CID)-based data-dependent MS collection mode. A 2 μL aliquot of the extracted material was introduced onto an inert sustain AQ-C18 (particle size: 3.0 μm; column size: 2.1 × 150 mm). A gradient of 2 %–98 % was employed using mobile phases A (0.1 percent formic acid in water, volume/volume) and B (acetonitrile). The constant flow rate and temperature were maintained at 200 μL/min and 40 °C, respectively. The data acquisition and peak annotation were done using the Compound Discoverer software version 3.3.2.31. The whole HR-MS omics run was done thrice for each technical replicate of the optimized UPPP-added yogurt sample.

2.4. Statistical analysis

All statistical calculations were done in triplicates and the obtained result was presented as the mean of the total values. The significance level of p-value less than 0.05 was applied in the one-way ANOVA for the comparison of the means. All work was executed by Microsoft Excel software.

3. Results and discussion

The present study aims to develop a functional yogurt with added green papaya peel powder and highlights the comprehensive metabolome profiling of the food product. During this work, the functional Greek yogurt was incubated with inoculation of two probiotic bacterial strains (i.e., *S. thermophilus* and *L. bulgaricus*), and with the incorporation of different concentrations of (0, 1.5, 2, 3, 6, 8, and 10 %) UPPP for the optimization process using sensory and textural investigation. We found that the T^3 treatment sample of yogurt having 3 % UPPP was the best optimized according to its appearance, flavor, texture, and overall acceptability in terms of sensorial attributes, and with the rheological attributes such as cohesiveness, hardness, gumminess, fracture ability, and chewiness using the cylindrical probe. After the completion of the LC-MS-based untargeted omics for the functional yogurt the results have shown a total of 1254 differential metabolites formed due to several types of interactions inside the yogurt matrix constituents. The total number of annotated peaks in the mass spectrum (Fig. 1) represents 43 specific compounds including the primary and secondary types of metabolites, and the 36 majorly expressed are shown in Table 1.

These metabolites can be categorized into organic acids, sugars, lipids, bioactive components, peptides, amino acids, fatty acids, and various types of derivatives, that have multiple types of physiological functioning in the human body such as antioxidative activity, antimicrobial, anti-diabetic, anti-inflammatory, anti-cardio vascular complication, anti-depressive, anti-septic, anti-biotic, anti-angiogenic,

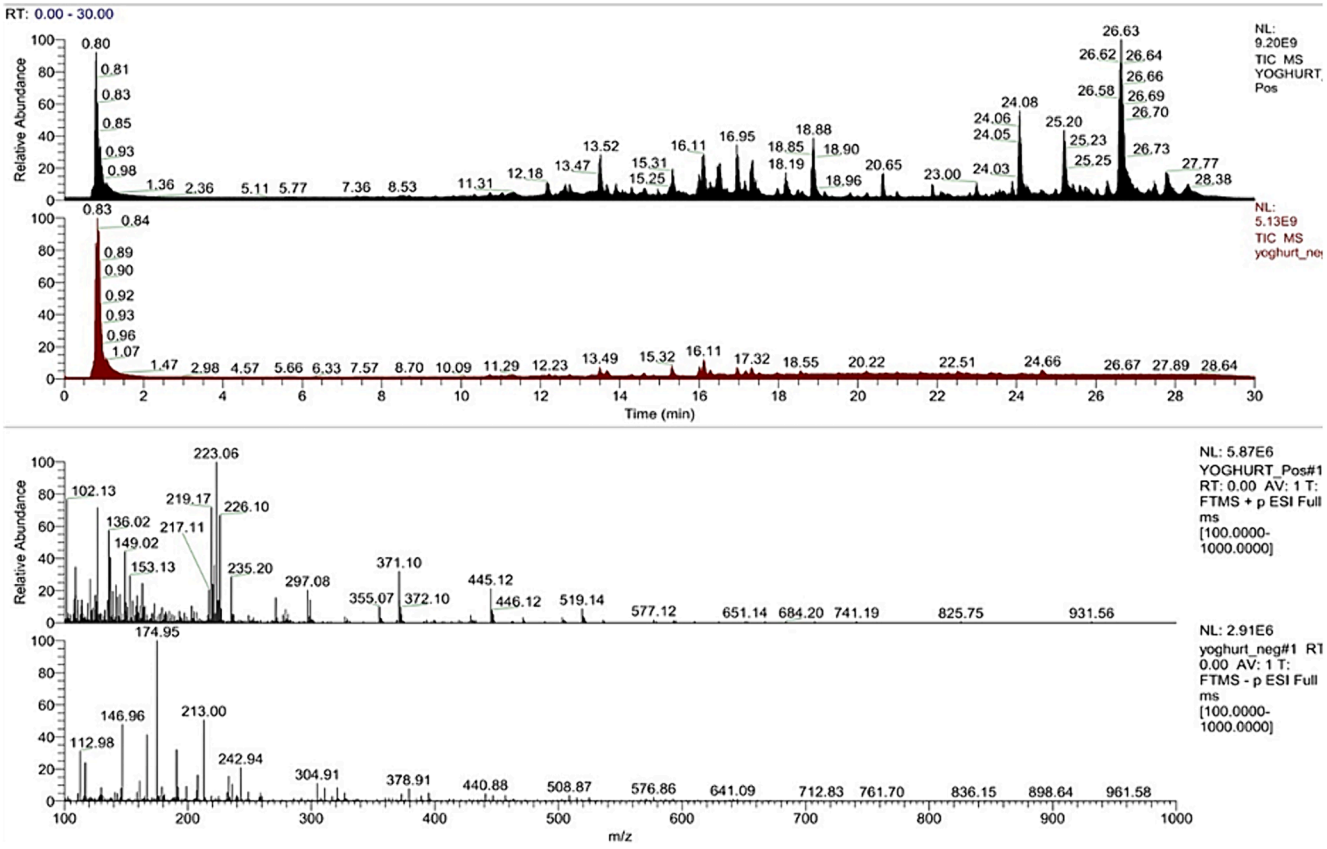

Fig. 1. The obtained mass spectrum from the high-resolution mass spectrometer-based metabolomics of Greek yogurt enriched with unripe papaya peel powder (T^3).

brain activity, neurogenerative, anti-carcinogenic, regulates homeostasis and lipid metabolism, metal ion chelation, antipyretic effect, osteoporotic prevention, immunomodulatory, etc. A detailed description of the majorly obtained metabolome compounds is given in Table 1 with their chemical formula, molecular weight, retention time (RT), the total area covered in the mass spectrum, and their respective functions.

Several earlier studies of this type have described the comprehensive metabolites profiling of different functional and processed food products, which reveals thousands of differential classes of metabolites. A metabolomics study conducted by Hiraga et al. (2021) on the unripe papaya pulp and peel has shown physiologically important metabolites such as alkaloids, carpamic acid, benzyl glucosinolate, and other polyphenol compounds. Putative carpaine derivatives, which are important papaya alkaloids were discovered by a study of the metabolic alterations between unripe and mature papaya fruits using metabolomic profiling (Cao et al., 2023). Selenocysteine has a lesser reducing capacity as compared to cysteine, and this characteristic makes it very prone to augmentation in the free radicals scavenging functions (Zoidis et al., 2018). Kaempferol augments human antioxidative activity against free radicals and also modulates apoptosis, angiogenesis, inflammation, and metastasis (Sharma et al., 2021). As a metabolite of aromatic chemicals from food, hippuric acid is an acyl glycine that is generated when benzoic acid and glycine conjugate. Hippuric acid is a typical component of urine and its concentration can have antibacterial properties (De Simone et al., 2021).

The metabolite quercetin has been known for attenuation of regressive action in various human health complications such as Alzheimer, diabetes, inflammation, Alzheimer, arthritis, oxidation activities, cardiovascular, microbial growth, and aiding as a wound-healer (Bhoi et al., 2023). The anti-carcinogenic action of quercetin metabolite against different cancer cell lines has also been revealed recently. Enhanced propionyl carnitine is regarded as a biomarker of vitamin B-12 deficiency. Ostruthin has its role in anxiety and depression control which are common mental disorders (Okada et al., 2020). Resorcinol is used in cosmetic pharmaceutical products as an anti-septic and infectant removal for the cure of skin problems and infections such as acne, seborrheic dermatitis, eczema, psoriasis, corns, calluses, and warts (Fabri et al., 2023). Monolaurin is a metabolite made from lauric acid, available in coconut oil and human breast milk, and is widely used in the prevention of the common cold, flu (influenza), shingles (herpes zoster), and other infections, but no ample number of scientific evidence are there to support this (Downs et al., 2023). The combination of monolaurin and lauric acid owing to the broad spectrum anti-microbial activities (Nitbani et al., 2022). Nitrofurantoin is an antibiotic medication in the line of treatment of uncomplicated lower excretory route infections. Palmitoleic acid ameliorates the action of controlling inflammatory disorder (de Souza et al., 2018).

Additionally, it has been observed from the obtained metabolome of the UPPP-incorporated Greek yogurt, that a few metabolites such as quercetin 5,7,3′,4′-tetramethyl ether 3-rutinoside (Chojnacka et al., 2020), and spisulosine (Ghosal & Shaw, 2010) have cancer-reducing potential that implies this developed yogurt is attributing the overall functionality. Nevertheless, a more concerned in-vivo study needs to be done for detailed scientific evidence of the anti-carcinogenicity of the UPPP yogurt. Campechic acid has anti-viral functionality that enhances its bioactivity (Jakubiec-Krzesniak et al., 2018). Oxanthromicin and amoricin are also known for exhibiting anti-microbial action as a bioactive compound (Wang et al., 2024; Kim YoungSoo et al., 2011).

The fortification of Greek yogurt with green papaya peel powder adds some content of dietary fibers in the gel matrix to this dairy product definitely, elucidating the potential symbiotic behavior of the product which owns probiotic microorganisms and prebiotics fibers.

Table 1
The major metabolites observed after high-resolution mass spectrometry of the functional Greek yogurt sample.

Sr. No.	Metabolites Name	Formula	Calc. MW	M/Z	RT (min)	Area	Functional properties
1.	Selenohomocystine	C8 H16 N2 O4 Se2	363.9442	362.9369	0.741	15,078,786	Antioxidant
2.	Gericudranin C	C22 H18 O8	410.0993	445.0686	0.779	13,584,806	Anti-CVD
3.	Pestalachloride C	C21 H20 Cl2 O5	422.0667	421.0594	0.87	4,838,997	Antifungal
4.	Kaempferol 3-sulfate-7-alpha-arabinopyranoside	C20 H18 O13 S	498.0474	497.0401	0.901	9,468,315	Antioxidant
5.	Phthalic anhydride	C8 H4 O3	148.0155	149.0228	6.128	52,060,017	Anti-alergic
6.	L-Histidine	C6 H9 N3 O2	155.069	156.0762	6.246	4,676,196	EAA
7.	Kaempferol 3-p-coumarate	C24 H16 O8	432.0842	433.0915	6.28	25,397,993	Anti-inflammatory
8.	Choline	C5 H13 N O	103.0995	104.1067	6.341	7.24E + 08	Brain activity
9.	Acetyl-β-methylcholine	C8 H17 N O2	159.1254	160.1327	6.355	76,931,308	Bronchial hyperreacticity
10.	Quercetin 5,7,3′,4′-tetramethyl ether 3-rutinoside	C31 H38 O16	666.2189	667.2263	6.388	66,920,084	Antidiabetic, Anti-cacinogenic
11.	Propionylcarnitine	C10 H19 N O4	217.1305	218.1378	6.59	43,148,080	HypospadiaIndication
12.	Butyryl-L-carnitine	C11 H21 N O4	231.1463	232.1536	8.106	1.12E + 08	Lipid metabolism
13.	Hippuric acid	C9 H9 N O3	179.0576	180.0649	9.461	57,869,764	Anti-bacterial
14	Oxanthromicin G	C31 H24 O9	540.1406	539.1333	0.805	68,953,643	Antifungal
15.	Ostruthin	C19 H22 O3	298.1572	297.1499	21.722	1.31E + 08	Anti-depressive, anxiolytic
16.	Resorcinol	C18 H34 O2 Si2	338.2096	337.2023	23.948	13,372,328	Anti-septic
17.	N-palmitoleyl glutamine	C21 H38 N2 O4	382.283	381.2757	24.406	25,767,298	Anti-CVD
18.	Syringolin	C24 H41 N5 O6	495.3041	496.3113	24.663	6,634,440	Anti-tumor
19.	Decanamide	C10 H21 N O	171.1618	172.169	25.84	9,244,468	Cleaning of water
20.	Epostatin	C23 H33 N3 O5	431.2421	432.2494	26.28	13,508,049	Protease inhibitor
21.	Saquayamycin	C43 H49 N O16	835.3053	836.3126	26.746	3,575,259	Anti-biotic
22.	Amoricin	C31 H36 O6	504.2526	505.2598	7.316	47,914,663	Antibacterial
23.	Saptomycin B	C41 H52 N2 O9	716.3648	715.3575	8.284	11,257,715	antitumor antibiotics
24.	Monolaurin	C15 H30 O4	274.2133	257.21	27.762	71,813,184	Anti-microbial
25.	Nitrosoxacin	C14 H30 N2 O2	258.2298	259.2371	28.069	4,534,164	Anti-biotic
26.	Palmitoleicacid	C16 H30 O2	254.2235	237.2203	28.395	11,025,663	Anti-inflammatory
27.	Formicolide	C33 H48 O8	572.3324	590.3663	28.626	8,653,715	Anti-oxidative, Anti-angiogenic
28.	catechin 3-tetradecanoate	C29 H40 O7	500.2756	523.2647	28.758	12,610,909	Help in weight loss
29.	Palmitoleic acid	C16 H30 O2	254.2235	255.2308	28.792	14,270,922	Anti-inflammatory
30.	α-Linolenic acid	C18 H30 O2	278.2236	279.2309	29.313	24,057,771	Anti-diabatic
31.	Glyceryl monoricinoleate	C21 H40 O5	372.2861	355.2829	29.691	1.99E + 08	Anti- CVD
32.	2-Oxooctadecanoicacid	C18 H34 O3	298.2495	299.2568	29.897	11,352,474	Anti-septic
33.	Spisulosine	C18 H39 N O	285.3021	286.3093	26.372	13,668,740	Anti-cancer
35.	1-Linoleoyl glycerol	C21 H38 O4	354.2757	355.283	30.876	38,040,074	Anti-CVD
36.	Palmitoleic acid	C16 H30 O2	254.2236	255.2309	27.631	11,496,954	Control inflammatory disorder

*Calc. MW: Calculated molecular weight; M/Z: Mass/Charge; RT: Retention time; CVD: Cardiovascular disease; EAA: Essential amino acid.

4. Conclusion

This study is the first attempt at untargeted metabolites profiling of an unripened papaya peel powder incorporated yogurt using the liquid chromatography-mass spectroscopy approach. The various metabolites annotated in the product reveal this new functional dairy product is owing good functional and therapeutic value. The green papaya peel powder has been added as a functional ingredient that yields a large number of bioactive components in the Greek yogurt matrix. Untargeted metabolomics equipped with high-resolution mass spectrum search is a reliable, rapid, and sophisticated tool for the detailed identification of the metabolites present in different functional dairy products worldwide. From the perspective of dairy science, foodomics could be widely utilized in the characterization and quantification of the metabolites in milk and milk products and has the power to revolutionize the dairy industry by providing a mechanistic tool for evaluating the quality and safety of the developed functional product by the valorization of by-products.

CRediT authorship contribution statement

Sohan Lal Bajya: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Durga Shankar Bunkarb:** Validation, Supervision, Resources, Methodology. **Sunil Kumar Goyal:** Supervision. **Manish Kumar Singh:** Writing – review & editing, Visualization. **Vinod Kumar Paswan:** Writing – review & editing. **Shankar Lal:** Writing – review & editing. **Priya Dhyani:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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