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Khalid Hussain Salaria
Natural Products-cum-Nano laboratory, Division of Biochemistry, Faculty of Basic Sciences, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Main campus Chatha, Jammu, Jammu and Kashmir, India

Sanjay Guleria
Natural Products-cum-Nano laboratory, Division of Biochemistry, Faculty of Basic Sciences, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Main campus Chatha, Jammu, Jammu and Kashmir, India

Aasiya Majeed
Natural Products-cum-Nano laboratory, Division of Biochemistry, Faculty of Basic Sciences, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Main campus Chatha, Jammu, Jammu and Kashmir, India

Pooja Choudhary
Natural Products-cum-Nano laboratory, Division of Biochemistry, Faculty of Basic Sciences, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Main campus Chatha, Jammu, Jammu and Kashmir, India

Faiqa Aiman
Natural Products-cum-Nano laboratory, Division of Biochemistry, Faculty of Basic Sciences, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Main campus Chatha, Jammu, Jammu and Kashmir, India

Corresponding Author:
Khalid Hussain Salaria
Natural Products-cum-Nano laboratory, Division of Biochemistry, Faculty of Basic Sciences, Sher-e-Kashmir University of Agricultural Sciences and Technology of Jammu, Main campus Chatha, Jammu, Jammu and Kashmir, India

Augmentation of polyphenol content and bioactive property of *O. sanctum* (Leaf) Methanolic extract using *Lactobacillus plantarum* (MTCC-1407)

Khalid Hussain Salaria, Sanjay Guleria, Aasiya Majeed, Pooja Choudhary and Faiqa Aiman

Abstract
In the present study, probiotic bacteria *L. plantarum* (MTCC-1407) was used for augmenting polyphenol content, antioxidant and anti-tyrosinase activity of *O. sanctum* methanolic extract. Optimization of fermentation parameters namely, inoculum load, pH, temperature and incubation time was done. DPPH radical scavenging activity and reducing power assays were performed for determining the antioxidant activity. Tyrosinase inhibitory activity assay was carried out to evaluate anti-melanogenesis property of plant extract. Results indicated that the optimized fermentation parameters *viz.*, inoculum load was 3.55 Log CFU/mL, pH was 6.5, temperature was 37 ºC and incubation time was 42 h. TPC was increased by 16.66 percent, TFC was enhanced by 24.25 percent, DPPH radical scavenging activity was increased by 4.54 percent reducing power was augmented by 4.00 percent and tyrosinase inhibitory activity was increased by 40.20 percent. These results provide the foundation for further exploration of the therapeutic and functional benefits of *L. plantarum* (MTCC-1407) mediated fermentation of *O. sanctum* methanolic extract. Furthermore, fermentation based biotransformation can be used as an alternative natural mechanisms for improvement of phytochemical constituents and bioactive properties of methanolic extract of *O. sanctum*.

Keywords: Fermentation, polyphenol content, antioxidant activity and anti-melanogenesis property

1. Introduction
Fermentation is a biological process that involves a series of biochemical events to convert organic metabolites into useful end products (Khirwadkar *et al.*, 2014; Smitha *et al.*, 2017) [1, 2]. Microbes are used as a biocatalyst to modulate organic chemical conjugates into optically pure and free forms of chemical derivatives in microbial induced fermentation of plant extracts, which is an evergreen and environmental friendly technology in biological sciences. It includes oxidation, condensation, hydrogenation, hydroxylation, isomerization, methylation, hydrolysis, reduction, glycosylation, and the synthesis of new carbon bonds, among other reactions (Nigam *et al.*, 2013; Smitha *et al.*, 2017; Salter *et al.*, 2019) [2, 3, 4]. Fermented plant extract (FPE) is a type of plant-based functional food that is widely consumed in China, Japan, and other Asian countries. FPE can be made from a variety of plants, including cereals, legumes, fresh fruits and vegetables, edible fungus. Plant extracts are fermented by microorganisms such as yeast, lactic acid bacteria (LAB), and acetic acid bacteria to produce a beverage or other physical forms (Blandino *et al.*, 2003) [5]. Traditional FPE products include pickles, bean paste, natto, miso, and so on. Whereas, most modern fermented plant extract (FPE) products are inoculated artificially.
Tulsi, or *Ocimum sanctum*, is a Lamiaceae plant. It has made a significant contribution to science both in ancient times and in modern studies due to its wide spectrum of medicinal properties. Tulsi is categorized as either vanya (wild) or gramya (cultivated) (grown in homes). Despite the fact that they serve the same purpose, the former has darker leaves. Wounds, bronchitis, liver illnesses, catarrhal fever, otalgia, lumbago, hiccough, ophthalmia, stomach disorders, genitourinary disorders, skin diseases, poisoning, and psychological stress disorders are all frequent home remedies for *Ocimum sanctum* (Das, 2006; Prajapati, 2003) [6, 7]. It also has aromatic, stomachic, carminative, demulcent, diaphoretic, diuretic, expectorant, alexiteric, vermifuge, and febrifuge properties (Gupta *et al.*, 2002) [8].
In view of above facts, a research problem was planned with the objective to investigate the potential of *L. plantarum* mediated fermentation of *O. sanctum* to enhance polyphenol content

antioxidant activity and anti-melanogenesis property of *O. sanctum* methanolic extract.

2. Materials and Methods

2.1 Collection of plant material

O. sanctum leaves were collected from Indian Institute of Integrative Medicine (IIIM) field station Chatha, Jammu, India.

2.2 Microbe used for fermentation process

Lactobacillus plantarum (MTCC-1407) used in the study was procured from National Chemical Laboratory (CSIR-NCL) Pune, Maharashtra, India.

2.3 *Lactobacillus plantarum* inoculum preparation

Lactobacillus plantarum inoculum preparation was carried out according to method of Salaria *et al.* (2021) [9]. *L. plantarum* (MTCC-1407) strain was obtained from the National Chemical Laboratory (CSIR-NCL) Pune, Maharashtra, India. The culture was activated at 37 °C for 24 h in 150 mL conical flasks containing 100 mL nutrient broth. *L. plantarum* cultivation was carried out statically in B.O.D until the cell density reached 782 which corresponds to 7.34 log colony forming units per millilitre (CFU/mL). Cell density was spectrophotometrically evaluated at 600 nm and this culture was used as inoculum in the fermentation processes.

2.4 Preparation of plant extract

Fresh plant part of *Ocimum sanctum* (leaves) were first washed using tap water followed by three times with distilled water and then allowed to dry in shade at room temperature. Shade dried plant parts were grounded to fine powder using a grinder (Model: Twister, Bajaj Electricals Ltd., Mumbai, India). Methanol was used as solvents for preparation of plant extracts. The plant extract were prepared by suspending 100 g of plant powder in methanol at room temperature and placed on rotary shaker at room temperature for 24 h. After 24 h the filtrate was collected in 500 mL of Erlenmeyer flask. The process was repeated thrice. Filtrate so obtained was concentrated to dryness by evaporating under reduced pressure at 45° C using vacuum rotary evaporator and preserved at 4° C until further use.

2.5 Optimization of fermentation parameters

Growth condition parameters for fermentation process of plant extract was optimized to assess optimum growth conditions and maximize efficiency of fermentation using shake flask method. Single parameter was optimized at one time while keeping other parameters constant. Optimization was done for inoculum load, pH, temperature and incubation time. Non-inoculated plant extract was maintained as control for comparison.

2.6 Analysis of total phenolic content (TPC)

Total phenolic content (TPC) of plant extract was estimated according to the method of Chang *et al.* (2001) [10] using gallic acid as standard with slight modification. Briefly 50 µL of plant extract was mixed with 950 µL of double distilled water to raise the volume up to 1mL. Then 1mL of 1N folin-ciocalteau's phenol reagent was added. Reaction mixture was shaken on vortex mixture which was followed by addition of 1 mL of 20% sodium carbonate (Na_2CO_3). After 30 minutes of incubation at room temperature absorbance was recorded at 730 nm using double beam UV-VIS spectrophotometer (Make: Labomed, USA).

Total phenolic content was derived from the equation obtained from the standard curve of gallic acid.

$Y=0.0395x+0.0879$: $R^2=0.998$

Total phenolic content was expressed as mg gallic acid equivalents per gram (mg GAE's/g) of plant extract.

2.7 Analysis of total flavonoid content (TFC)

Total Flavonoid content of non-fermented and fermented plant extracts was determined according to the method of Lamaison and Carnet (1990) [11] with slight modification using quercetin as reference. Briefly 100 µL of extract was mixed with 900 µL double distilled water followed by addition 75 µL of 5% sodium nitrite ($NaNO_2$) solution. Reaction mixture was then shaken using vortex mixture. After 5 minutes, 150 µL of 10% aluminium chloride solution was mixed and allowed to incubate for 6 minutes at room temperature followed by addition of 500 µL of 1M (NaOH) sodium hydroxide solution. Final volume of reaction mixture was raised up to 2.5 mL by adding 775 µL of double distilled water, after five minutes absorbance was recorded at 510 nm using double beam UV-VIS spectrophotometer.

Total Flavonoid content was derived from the equation obtained from standard curve prepared from quercetin.

$y= 0.0208x + 0.0395$: $R = 0.997$

Total flavonoid content was expressed as mg quercetin equivalents per gram (mg QE's/g) of dry weight.

2.8 Analysis of 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity

Antioxidant activity of non-fermented and fermented plant extracts was determined by measuring their scavenging effects DPPH. The radical scavenging activity was determined according to the method of Abe and others (1998) [12]. Different concentrations of non-fermented and fermented plant extracts were taken from 1 mg/mL stock solution and the volume was made to 1mL with methanol. Then 1 mL of 0.2 mM DPPH solution prepared in methanol was mixed with the extracts and final volume of the reaction mixture was raised to 4 ml by adding 2 mL of 0.1 M sodium acetate buffer (pH 5.8). The reaction mixtures were incubated in the dark for 30 minutes at 37 ºC. The absorbance was measured at 517 nm using double beam UV-Visible spectrophotometer. Methanol was used as a negative control. The radical scavenging activity (RSA) was calculated as a measure of the percentage of the decrease in absorbance or DPPH radical bleaching according to the following equation:

$$RSA\ (\%) = (1-A_{sample}/A_{blank}) \times 100$$

Where A_{blank} is the absorbance of the positive control (containing all the constituents of the reaction mixture except sample), and A_{sample} is the absorbance of the test sample. Absorbance decreases with increase in antioxidant activity. The concentration of extract at which absorbance becomes exactly half of that of the control is known as IC_{50}. It is that effective concentration of the extracts at which 50% radical

scavenging took place with respect to the control and was calculated from the graph by plotting percent radical scavenging activity (RSA) against extract concentration by taking (butylated hydroxytoluene) BHT as the reference compound.

2.9 Analysis of reducing power

The reducing ability of both non-fermented and fermented plant extracts was measured according to the method of Oyaizu with slight modifications (1986) [13]. Different concentrations of the fermented and non-fermented extracts were taken from their respective 1 mg/mL stock solutions prepared in methanol and volume was made to 1ml with methanol. 2.5 mL of 0.2 M phosphate buffer (pH 6.6) and 2.5 mL of 1% (potassium ferricyanide) K_3 Fe [CN_6] were then mixed with different doses of the fermented and non-fermented extracts. The reaction mixture was incubated at 50 °C for 30 minutes. After that 2.5 mL of 10% (w/v) trichloroacetic acid was added to the mixture. The whole reaction mixture was then centrifuged at 3000 rpm for 10 minutes. 2.5 mL of the upper layer of the centrifuged solution was then taken and was mixed with 2.5 mL of distilled water and 2.5 mL of 0.1% ferric chloride solution ($FeCl_3$). Absorbance of the reaction mixture was measured at 700 nm using a double beam UV-Visible spectrophotometer (Make: Labomed, USA). The assay was conduted in triplicate. Absorbance of the reaction mixture increased with the reducing power of the extracts. IC_{50} is the extract concentration at which 0.5 of absorbance was obtained and was calculated by plotting the graph of absorbance at 700 nm versus extract concentrations.

2.10 Analysis of tyrosinase inhibitory activity

The antityrosinase activity of non-fermented and fermented plant material extracts were analyzed with slight modification using the method reported by Zheng *et al.* (2012) [14]. The extract was dissolved in double distilled water (ddw) in a concentration of 1 mg/mL. 30 µL of methanolic extract was mixed with 970 µL of sodium phosphate buffer (0.05 mM) and subsequently added to 1 mL of 100 mg/L-tyrosine and 1 mL of mushroom tyrosinase (make Sigma Aldrich) solution (350 units/mL). All 3 mL of this reaction solution was homogeneously mixed and the absorbance was measured at 490 nm using double beam UV-visible spectrophotometer. The absorbance of the solution was measured at 490 nm after 20 minutes of incubation.

Antityrosinase activity of the methanolic extract is expressed as a percentage of tyrosinase inhibition using the following formula:

$$\text{Tyrosinase inhibition (\%)} = [(A-B)-(C-D)]/ (A-B)\times 100$$

Where A_{Sample} is the absorbance of the extract containing reaction and $A_{Control}$ the absorbance of the reaction control. Tests were carried out in triplicate and a blank with Tris-HCl buffer instead of enzyme solution was used.

3. Statistical analysis

All experiments were carried out in triplicates. The results were expressed as mean ± S.D. Analysis of variance was used to analyze the experimental data.

4. Results and Discussion

In the food sector, fermentation has been utilised to improve organoleptic and nutritional qualities (Kantachote *et al.*, 2008) [15]. Thus, using probiotic-based fermentation to induce effective microbial alterations of naturally occurring phytochemicals and the production of beneficial secondary metabolites can result in the detoxification of unwanted elements as well as the improvement of biological activity (Kim *et al.*, 2009) [16].

Phenolics are a collection of secondary metabolites found in plants that protect them from abiotic and biotic stressors, as well as help them grow and develop morphologically (Cosme *et al.*, 2020) [17]. Flavonoid is the largest class of phenolics, and it is principally responsible for plant colour and aroma (Khoddami *et al.*, 2013) [18].

Norakama *et al.* (2018) [19] reported significant enhancement in total phenolic content and antioxidant potential of *Kappaphycus alvarezii* extracts after optimization of fermentation parameters namely, inoculum load (10% V/V), pH (7), temperature (30 ºC) and incubation period (96 h) with *Aspergillus oryzae*. Similarly, Dewi *et al.* (2020) [20] carried out *L. acidophillus* mediated fermentation of *Gelidium sp.* extract using optimized fermentation parameters such as, 6% inoculum concentration at 37 ºC for 24 h. Likewise, Couto *et al.* (2017) [21] reported 3.1 times augmentation in curcumin after optimization of fermentation conditions namely, culture media, carbon source, and inoculum concentration with *E.ccoli.* Similarly, Tiku *et al.* (2017) [22] also reported increased total phenolic content and antioxidant potential of *Camella sinesis* leaves after optimization of fermentation conditions namely 35 minutes incubation period and 36 ºC temperature. Likewise, Kuo *et al.* (2021) [23] reported enhancement of total polyphenol content of LAB mediated fermentation of *Chenopodium formosanum* extracts using 24.4 ºC temperature, pH 5.5 and 104 rpm as fermentation parameters. Similarly, in the present study the fermentation parameters were optimized. The optimized inoculum load, pH, temperature and incubation time for *L. plantarum* mediated fermentation of *O. sanctum* methanolic extracts were 3.55 Log CFU/mL, 6.5, 37 ºC and 42 h respectively.

Wang *et al.* (2017) [24] carried out a study in which *Angelica dahurica* root extract was fermented with lactic acid bacteria, which enhanced polyphenol content and tyrosinase inhibitory activity of fermented extract in comparison to non-fermented extract. Similarly, Morais *et al.* (2019) [25] found that *L. acidophillus* fermented red pitaya pulp had higher bioavailability of phenolics and flavonoids than non-fermented red pitaya pulp. LAB fermented herbal plant extracts have also been shown to have increased total phenolic and flavonoid content as well as tyrosinase inhibitory activity (Wang *et al.*, 2016) [26]. Likewise, in the present study TPC increased by 16.66 percent in comparison to non-fermented extract as shown in table no. 1 and fig. no. 1. TFC enhanced by 24.25 percent in contrast to control as depicted in table no. 1 and fig. no. 2. Antioxidant activity which encompasses DPPH radical scavenging activity and reducing power increased by percent 4.54 and 4.00 percent respectively, in comparison to non-fermented extract as shown in table no. 2 and fig. no. 3 and 4. The tyrosinase inhibitory activity of *L. plantarum* mediated fermented *O. sanctum* methanolic extract enhanced by 40.20 percent in comparison to control as depicted in table no. 3 and fig. no. 5.

Table 1: Total phenolic (TPC) and total flavonoid (TFC) content of non-fermented and fermented *O. sanctum* methanolic extract by *L. plantarum*

Extract	TPC (GAE's mg/g dry weight)	TFC (QE's mg/g dry weight)
NF	60.33±1.25	25.24±2.43
F	72.39±0.72	33.41±2.66

Table 2: DPPH and reducing power of non-fermented and fermented *O. sanctum* methanolic extract by *L. plantarum*

Extract	DPPH IC_{50} (µg/ml)	Reducing power IC_{50} (µg/ml)
NF	106.54±1.79	317.05±2.49
F	101.70±0.89	304.34±1.85

Table 3: Tyrosinase inhibitory activity of non-fermented and fermented *O. sanctum* methanolic extract by *L. plantarum*

Extract	Tyrosinase inhibitory activity (%)
NF	23.44±0.64
F	39.20±0.44

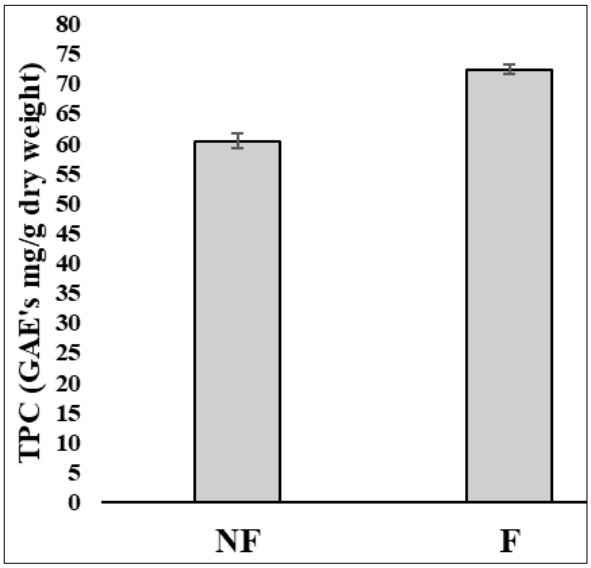

Fig 1: Difference between total phenolic content (GAEs mg/mL fresh weight) of *O. sanctum* methanolic extract non-fermented and fermented by *L. plantarum*

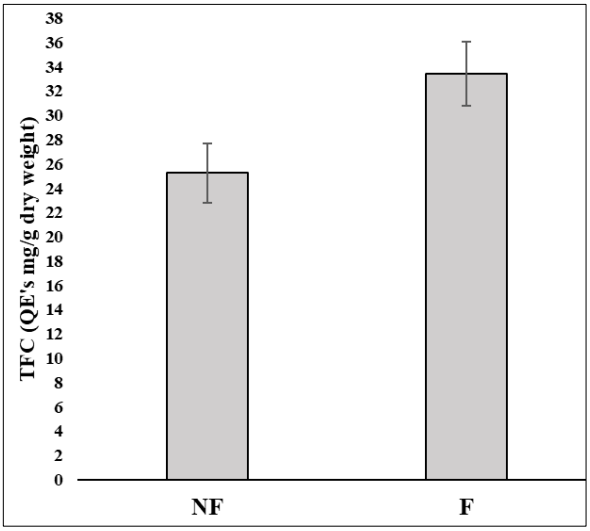

Fig 2: Difference between total flavonoid content (QE's mg/g dry weight) of *O. sanctum* methanolic extract non-fermented and fermented by *L. plantarum*

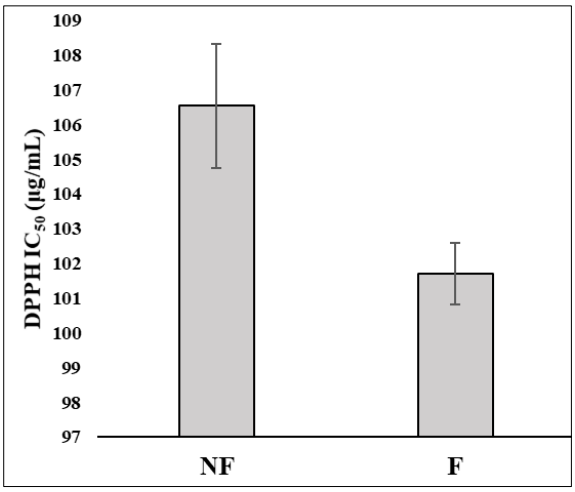

Fig 3: Difference between DPPH IC_{50} (µg/mL) of *O. sanctum* methanolic extract non-fermented and fermented by *L. plantarum*

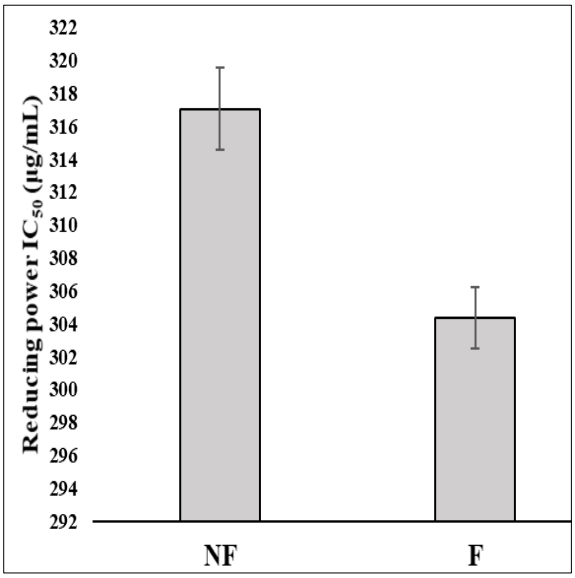

Fig 4: Difference between reducing power IC_{50} (µg/mL) of *O. sanctum* methanolic extract non-fermented and fermented by *L. plantarum*

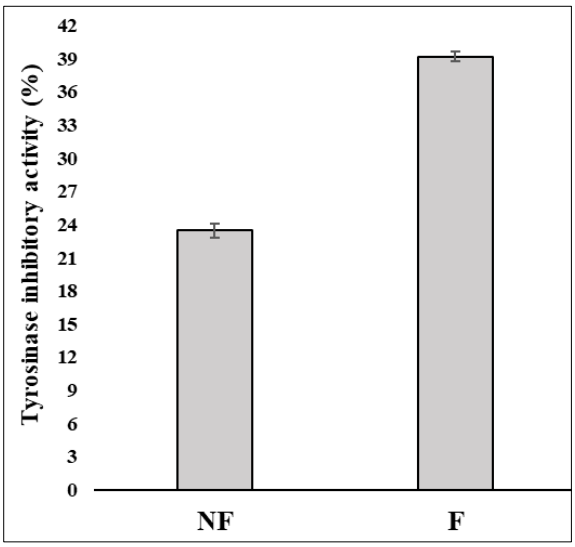

Fig 5: Difference between Tyrosinase inhibitory activity (%) of *O. sanctum* methanolic extract non-fermented and fermented by *L. plantarum*

5. Conclusion

It can be concluded from the present study that fermentation based biotransformation can be used as an alternative natural mechanisms for improvement of phytochemical constituents and bioactive properties of methanolic extracts of *O. sanctum*. Probiotic microbe mediated fermentation of methanolic *O. sanctum* extracts resulted in enhancement of total phenolic content (TPC), total flavonoid content (TFC) strongest 2,2-diphenyl-1-picrylhydrazyl (DPPH), radical scavenging activity, reducing power, anti-tyrosinase activity which may have therapeutic and nutritional applications.

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