Indo Global Journal of Pharmaceutical Sciences, 2023; 13: 1-12

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

A Review on Pharmacological Activities of Vanillic Acid and its Derivatives

Anil Malik, Anurag Khatkar, Saloni Kakkar *

Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, India

Address for Correspondence: Saloni Kakkar, salonikakkar2007@gmail.com

Received: 11.02.2020
Accepted: 21.07.2020
Published: 13.02.2023
Keywords
Phenolic acids; vanillic acid; antimicrobial; antioxidant; anticancer; anti-inflammatory; antidiabetic; antinociceptive.

ABSTRACT: Vanillic acid is a type of phenolic acid which occurs widely in natural products. As phenolic acids possess a lot of pharmacological activities, a number of extracts from different natural sources containing vanillic acid were checked for their various biological profiles by different methods. Vanillic acid was found as a good antimicrobial, antioxidant, anticancer, antidiabetic, anti-inflammatory, antiulcer and antinociceptive agent. Vanillic acyl hydrazone derivatives were found as novel antimicrobial compounds.

INTRODUCTION

Reactive oxygen species (ROS) are the major factors for aging and death of cells [1]. In the body, they may generate from several metabolic processes, ultraviolet radiation and other biochemical reactions [2]. These ROS and free radicals produced from oxidative stress may cause degradation of DNA, lipids, proteins and carbohydrates and cause many serious diseases like cancer and diabetes [3]. Antioxidants have the capability of scavenging various ROS species like hydroxyl radicals (OH), superoxide anion radicals (O_2^-) and hydrogen peroxide (H_2O_2) and thus prevent cells from oxidative degradation [4]. Antioxidants obtained from natural products like fruits, vegetables and other natural sources have less side effects and are very potent in diminishing oxidative stress by scavenging free radicals [5] and keep balance among antioxidants and oxidants [6].

Diabetes Mellitus is a very serious disease of endocrine gland in which there is a disturbance in the metabolism of carbohydrates and lipids [7]. Oral hypoglycemic agents used have many serious side effects. So, there is a great need to discover novel and safe hypoglycemic drugs for the treatment of diabetes mellitus [8].

The activity to inhibit the carbohydrate-hydrolyzing enzymes like *α-amylase* is becoming an effective technique to treat type 2 diabetes by blocking the glucose absorption [9]. *α-Amylase* inhibitors retard the rate of starch breakdown and further postprandial blood glucose levels. *α-Amylase* occurs in saliva, pancreatic juice and is a protein enzyme. It breaks alpha bonds of polysaccharides like glycogen, starch and hydrolyses them into glucose and maltose [10]. Synthetic antidiabetic drugs have various side effects and this leads to discover new, safe and natural drugs [11]. Phenolic compounds among natural sources are found to possess good *α-amylase* and *α-glucosidase* inhibitory activity [12].

Urease is a nickel containing enzymatic protein which is also the first crystallized enzyme [13]. *Urease* is widely distributed in water, soil and human body [14]. Sources of *urease* are plants, bacteria [13], fungi [15] and some invertebrates [16]. In human body it helps in hydrolysis of urea [17]. *Urease* in high amount is harmful for human tissues and may cause or elevate several diseases like

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

rheumatoid arthritis or atherosclerosis [18]. It is found in human sera as an immunogenic protein and acts as antibodies. *Urease* is also required by various pathogenic bacteria for maintaining their cells in tissues. Ureolytic activity is responsible for various bacterial infections [19]. *Urease* is also used for diagnostic purposes. Ureolytic activity is used to diagnose the *Helicobacter pylori* infection. Bacterial *urease* causes many biological disorders like gastritis, peptic ulcers [20], kidney stones [21] and also cardiovascular disease [22].

Natural products have been used as source of medicines from a very long time [23]. Phenolic acids possess numerous biological activities like antioxidant [24] and anticancer activities [25]. After administration phenolic acids get absorbed very quickly [26]. Among all the phenolic acid contents vanillic acid is a compound of great interest as it possesses numerous biological activities like antioxidant [27], antimicrobial [28], anti-inflammatory [29], anticancer [30], antidiabetic [31] and antinociceptive activities [32]. Vanillic acid was also found to possess several other activities like anticoagulant [33], antiulcer [34], inhibitory effect on methylglyoxal-mediated glycation in apoptotic Neuro-2A cells, nephroprotective effect [35] and also prevents deregulation of lipid metabolism [36].

Vanillic acid also known as 4-hydroxy-3-methoxybenzoic acid is a white to yellow white powder or crystals, molar mass - 168.14 g/mol having the molecular formula $C_8H_8O_4$ [37]. The highest amount of vanillic acid in plants known so far is found in the root of *Angelica sinesis* [38**]**. Acai oil, obtained from the fruit of acai palm (*Euterpe Oleracea*) is an enriched source of vanillic acid (1616 ± 94 mg/kg) [39**]**. Vanillic acid can also be synthesized from vanillin by silver oxide method [40].

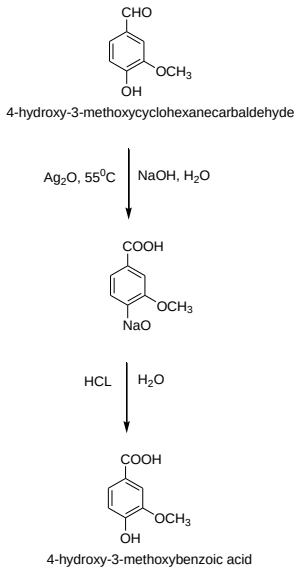


Fig 1: Synthesis of vanillic acid from vanillin

SOURCES OF VANILLIC ACID

Table 1 covers the key sources of vanillic acid along with their biological activity reported there.

Table 1: Sources of 4-hydroxy-3-methoxy benzoic acid

S.NO.	Species (Family)	Part used	Biological activity	Reference
1.	*Tamarix gallica* (Tamaricaceae)	Leaves, flowers	Antimicrobial	41
2.	*Lawsonia inermis* (Lythracea)	Leaves	Antimicrobial	42
3.	Mushroom (Morchellaceae)	Stem	Antimicrobial	43
4.	*Saccharum officinarum (Poaceae)*	Bagasse	Antimicrobial	44
5.	*Thymelaea hirsute* (Thymelaeaceae)	Leaves	Antimicrobial	45
6.	*Vitis vinifera* (Vitaceae)	Fruit	Antimicrobial	46
7.	*Onosma hispidum* (Boraginaceae)	Root bark	Antimicrobial	47
8.	*Rhizopus oligosporus* (Mucoraceae)	Bran	Antioxidant	48
9.	*Panax ginseng* (Araliaceae)	Seed	Antioxidant	49
10.	*Rosa canina* (Rosaecae)	Fruit	Antioxidant	50
11.	*Vigna radiate* (Fabaceae)	Seeds	Antioxidant	51
12.	*Ricinus communis* (Euphorbiaceae)	Seeds	Antioxidant	27
13.	*Chenopodium album* (Amaranthaceae)	Fruit, leaves	Antioxidant	52
14.	*Triticum aestivum* (Triticaceae)	Seeds	Antioxidant	53
15.	*Vigna mungo*	Seeds	Antidiabetic	54

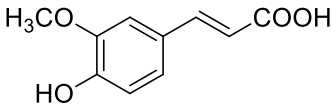
Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

	(Leguminosae)			
16.	*Pyrus* (Rosaceae)	Peel, pulp	Antidiabetic	55
17.	*Chenopodium quinoa* (Amaranthaceae)	Seed	Antidiabetic	56
18.	*Nerium oleander* (Apocynaceae)	Leaf	Antidiabetic	57
19.	*Euonymus alatus* (Celastraceae)		Antidiabetic	58
20.	*Aerva lanata* (Amaranthaceae)	Plant	Antidiabetic	8
21.	*Polygonum bistorta* (Polygonaceae)	Leaves, roots	Anticancer	59
22.	*Salvia rosmarinus* (Lamiaceae)	Leaves	Anticancer	60
23.	*Eucalyptus camaldulensis* (Myrtaceae)	Leaves	Anticancer	61
24.	*Oryza sativa* (Poaceae)	Seeds	Anticancer	62
25.	*Truffles* (Tuberaceae)	Fruit	Anti-inflammatory	63
26.	*Dendropanax morbifera* (Araliaceae)	Leaves	Anti-inflammatory	64
27.	*Plantago reniformis* (Plantaginaceae)	Leaves	Anti-inflammatory	65
28.	*Balanites aegyptiaca* (Zygophyllaceae)	Bark	Anti-inflammatory	66

BIOLOGICAL PROFILE OF VANILLIC ACID AND ITS DERIVATIVES

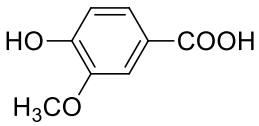
1. Antimicrobial activity

Naz *et al.* evaluated the antibacterial potential of ethanolic extract of root bark of *Onosma hispidum*. Major compounds reported in the extracts were 4-hydroxy-3-methoxy cinnamic acid [1] and 4-hydroxy-3-methoxy benzoic acid [2]. Agar well diffusion assay method was used to check the antimicrobial activity of extract. Concentration of the extract sample was taken as 0.5 µg. Extract showed a good inhibition activity against all gram positive bacteria with a complete inhibition zones of 20, 19, 20, 20, 20, 18, 20, 18,18, 20 and 20 mm against *Corynebacterium diptheriae*, *Corynebacterium diptheriticum*, *Micrococcus lysodiecticus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Enterococcus faecalis* 2400, *Enterococcus faecium*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* respectively in agar wells. No activity was reported against gram negative bacteria (47).



4-Hydroxy-3-methoxy-cinnammic acid (ferulic acid)

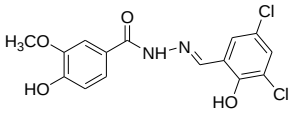
(1)



4-Hydroxy-3-methoxy benzoic acid (vanillic acid)

(2)

Wang *et al*. carried out a study to determine the antibacterial activities of vanillic acyl hydrazone derivatives. 30 derivatives were synthesized from vanillic acid (2) and were investigated to inhibit two Gram-positive (*Staphylococcus aureus* ATCC 6538 and *Bacillus subtilis* ATCC 530) and Gram negative (*Escherichia coli* ATCC 27853 and *Pseudomonas aeruginosa* ATCC 27853) bacterial strains. Among all the studied 30 vanillic acyl hydrazone derivatives, (E)-N'-(3,5-dichloro-2-hydroxybenzylidene)-4-hydroxy-3-methoxybenzohydrazide was found to possess highest antibacterial activity with minimum inhibitory concentration (MIC) values of 1.56, 0.78, 0.39 and 0.39 µg/mL against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* respectively [67].



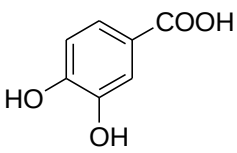
(*E*)-*N*'-(3,5-dichloro-2-hydroxybenzylidene)-4-hydroxy-3-methoxybenzohydrazide

(3)

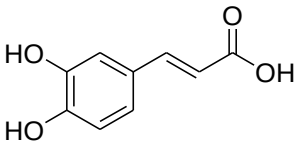
Nowacka *et al*. determined the number of phenolic constituents along with antimicrobial ability of edible mushrooms extracts. Vanillic (2), protocatechuic (4), caffeic (5), *p*-coumaric (6) and ferulic acids (1) were chiefly found phenolic compounds in mushroom extracts. Antimicrobial assay of 19 different mushrooms was performed by the micro-broth dilution method. Strains used were gram negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*) and gram positive bacteria (*Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*). The minimum inhibitory concentration (MIC) values of all the extracts were found to lie within the range from 1.25

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

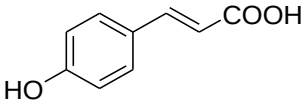
to 5 mg/ml. *Armillaria mellea*, *Corpinus micaceus*, *Lactarius rufus* and *Xerocomus badius* were found as the most active antibacterial mushrooms with MIC value 0.625 mg/ml against *Micrococcus luteus* [43].



Protocatechuic acid
(4)

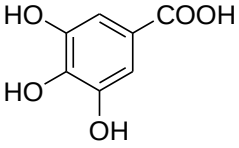


Caffeic acid
(5)

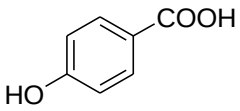


p-coumaric acid
(6)

Oliveira *et al.* studied the antimicrobial and antifungal activity of grape (*Vitis vinifera*) pomace extracts. The extracts were found to contain gallic acid (7), *p*-hydroxy benzoic acid (8) and vanillic acid (2) as phenolic contents which were determined by HPLC. The activity was checked against gram positive (*Staphylococcus aureus* and *Bacillus cereus*) and gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*). Three fungi strains used were *Candida albicans, Candida prapsilosis* and *Candida krusei.* Agar Diffusion method (ADM) was used to check the antibacterial activity and microdilution method was used to determine the antifungal activity. Merolet extract prepared at 50^0C/150 bar showed inhibition zone of 12 and 11 mm against *Staphylococcus aureus* and *Bacillus cereus* respectively and extract prepared at 60^0C/250 bar showed inhibition zone at 10 mm for both *Escherichia coli* and *Pseudomonas aeruginosa*. In case of antifungal activity extract prepared at 50^0C/200 bar gave minimum inhibitory concentration (MIC) values of 500 µg/ml, 1000 µg/ml, 500 µg/ml and extract prepared at 60^0 C/150 bar gave MIC values of >2000 µg/ml, 2000 µg/ml and 1500 ± 500 µg/ml against *Candida albicans, Candida prapsilosis* and *Candida krusei* respectively [46].

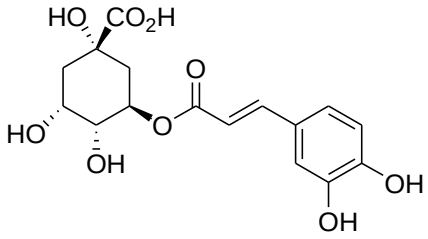


Gallic acid
(7)

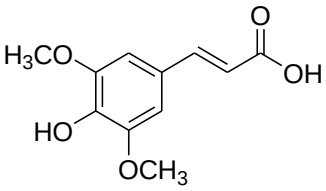


p-hydroxybenzoic acid
(8)

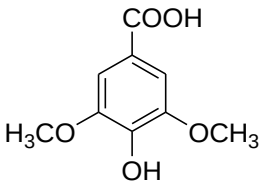
Ksouri *et al.* evaluated the phenolic contents and antimicrobial activity of edible medicinal halophyte *Tamarix gallica* L. Phenolic compounds were checked by RP-HPLC which showed the presence of 12 phenolic compounds having vanillic (2), chlorogenic (9), sinapic (10), gallic (7) and syringic acid (11). The antimicrobial activity of leaf and flower extract was determined by agar disk diffusion assay on five pathogenic bacteria including Gram negative bacteria namely *Escherichia coli*, *Pseudomonas aeruginosa* and Gram positive bacteria were *Staphylococcus aureus, Staphylococcus epidermidis* and *Micrococcus luteus*. Mean inhibition zone was found as 4 mm for flower extract and 2.7 mm for leaves extract in case of all bacteria. An increment in inhibition zone was observed from 0 – 6.5 mm when the concentration of the extract was increased from 2 to 100 mg/ml [41].



Chlorogenic Acid
(9)



Sinapic acid
(10)



Syringic acid
(11)

A study was carried out to determine the antimicrobial activity of sugarcane (*Saccharum officinarum* L.) bagasse extract towards food-borne pathogens by Zhao *et al.* The extract was found to contain different phenolic compounds in which vanillic acid (2) was 0.62 ± 0.09 mg/g. Antibacterial activity of the extract was analyzed using the oxford cup method against the Gram-positive bacteria *Staphylococcus aureus*, *Listeria monocytogenes* and Gram-negative bacteria *Salmonella typhimurium* and *Escherichia coli.* The minimum inhibitory concentration of the extract was found as 0.625, 1.25, 2.50 and 2.50 mg/ml against *Staphylococcus aureus, Listeria monocytogenes*, *Escherichia coli* and *Salmonella typhimurium* respectively [44].

Cueva *et al.* checked the antimicrobial profile of different phenolic acids including vanillic acid (2) against certain pathogenic and probiotic bacteria including *Candida albicans, Pseudomonas aeruginosa, Staphylococcus aureus, Lactobacillus spp. and Escherichia coli*. Antimicrobial assay was done by checking the percent growth inhibition of the bacteria in the specific inoculum prepared. Vanillic acid showed a maximum inhibition of 89.86% against *Lactobacillus paraplantarum* and 31.83% against *Lactobacillus coryniformis* at a concentration of 1000 µg/ml [68].

A study was done to analyze the antimicrobial activity chemical composition of acetone and ethanol extract of *Tunisian Thymelae hirusta* by Trigui *et al*. Phenolic contents reported in the extract were vanillic acid (2), ferulic acid (1),

caffeic acid (5) and gallic acid (7). Antimicrobial assay was done by agar well diffusion method. Minimum inhibitory concentration (MIC) to inhibit the growth for Gram positive bacteria was found as 0.312, 0.156, 0.625, 0.625 and 0.625 µg/ml for *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *Micrococcus luteus* and *Listeria monocytogenes* respectively. MIC values for Gram negative bacteria were 1.25, 2.5, 0.625 and 0.312 µg/ml for *Salmonella enterica*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* respectively [45].

Dhaoudi *et al*. carried out a study to evaluate the phytochemical composition and antibacterial activities of leaves and processed powder extract of Henna (*Lawsonia inermis* L.). Among phenolic contents reported, the concentration of ester of vanillic acid (2) was found as 1.46 µg/g. Antibacterial activity was evaluated using agar diffusion assay against different bacterial strains. The minimum inhibitory concentration (MIC) values of henna's powder (HP) and leaves (HL) found are given below in **Table 2** [42].

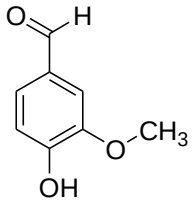
Table 2: Minimum inhibitory concentration of HL and HP extract of Henna

Bacterial Strains	HL extract	HP extract
B. subtilis	109.5 ± 4.9	41.1 ± 0.5
S.aureus	54.3 ± 1.8	41.1 ± 0.5
C. albicans	109.5 ± 4.9	84.3 ±3.8
E. coli	219 ± 10	674.7 ± 30.7
P. aeruginosa	219 ± 10	165.8 ± 3.7
L. monocytogenes	219± 10	21.5 ± 6.9

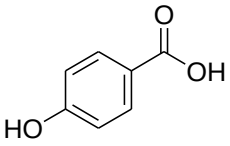
Crude extract of Myrtle (*Myrtus communis* L.) was investigated for its antimicrobial activity by Aleksic *et al*. Leaves extract of Myrtle was found to possess high content of phenolic acids. Activity was evaluated using two methods namely broth dilution method and agar diffusion method. Gram positive bacteria namely *Staphylococcus aureus*, *Micrococcus luteus* and Gram negative bacteria namely *Escherichia coli* were used. Minimum inhibitory concentration values of the crude extract were found as 0.1 mg/ml for *Staphylococcus aureus*, *Micrococcus luteus* and 2 mg/ml for *Escherichia coli* [69].

2. **Antioxidant activity**

Mourtzinos *et al*. carried out a study to find the thermal effect on the antioxidant activity of mixture of vanillin (12) and vanillic acid (2). DPPH free radical assay method was used to determine the free radical scavenging activity of the sample. Sample was heated at different temperatures at time intervals of 10-90 minutes in a Perkin- Elmer DSC instrument and activity was checked at different temperatures. Radical scavenging percent of thermally treated sample was found 11.4 ± 0.53 % at 131^0 C, 13.7 ± 0.31 % at 210^0 C and 20.6 ± 1.15 % at 262^0 C. Results revealed that there was an increase in radical scavenging activity of vanillin- vanillic acid mixture on increase of temperature due to formation of vanillic acid from vanillin [70].



Vanillin
(12)



4-hydroxybenzoic acid
(13)

Razak *et al*. checked the enhancement in the antioxidant activity of phenolic content of fermented rice bran (RB) against the non-fermented part of RB (**Table 3**). Fermentation of rice bran was done by *Rhizopus oligosporus* and *Manascus purpureus* fungi. Phenolic contents reported in rice bran were ferulic acid (1), sinapic acid (10), vanillic acid (2), caffeic acid (5), syringic acid (11) and 4-hydroxybenzoic acid (13). Antioxidant activity was determined using the ferric reducing ability of plasma (FRAP) and DPPH (2,2-diphenyl-1-picrylhydrazyl) methods. Results revealed that there was a significant increase in the antioxidant activity of phenolic content of the fermented rice bran than non-fermented part [48].

Table 3: Radical-scavenging activity (DPPH) and FRAP of methanol and water extracts of rice bran (RB).

Sample	Extracts	FRAP (µg AAE/g sample)	DPPH (% scavenging activity)
Non-fermented	Methanol	30.93 ± 3.80	87.51 ± 1.19
	Water	30.22 ± 9.57	87.82 ± 2.41
M. purpureus	Methanol	61.44 ± 0.98	90.19 ± 0.77
	Water	116.33 ± 4.74	91.75 ± 1.11
R. oligosporus	Methanol	80.68 ± 1.07	66.02 ± 0.13
	Water	61.21 ± 4.50	85.14 ± 0.12
R. oligosporus + *M. purpureus*	Methanol	74.75 ± 1.18	73.80 ± 1.88
	Water	144.03 ± 10.12	44.01 ±1.14

Eom *et al*. determined the antioxidant activity of eight types of differently substituted phenolic acid conjugated chitooligosaccharides (PA-c-COSs). Eight types of PA-c-COS from vanillic acid (2), ferulic acid (1), hydroxybenzoic acid (8), protocatechuic acid (13), *p*-coumaric acid (6), caffeic acid (5), sinapic acid (10) and

syringic acid (11) were made by amide coupling reaction. DPPH, hydroxyl (*OH) and nitric oxide radical scavenging methods were used for antioxidant evaluation. In observation, among all the eight PA-c-COSs, caffeic acid (CFA-c-COS) was found to be most active radical scavenging agent against DPPH, NO and hydroxyl radicals. Its scavenging activity was measured 89.8 % against nitric oxide and 81.6 % against DPPH radicals [71].

Reddy *et al*. determined the total antioxidant activity of previously synthesized phenolic moieties – ferulic (1) and vanillic acid (2) by DPPH radical scavenging assay. α-Tocopherol, dodecyl gallate and butylated hydroxyl toluene (BHT) were used as standards and were taken in the same concentration as that of phenolic compounds. Both the compounds were found to possess following antioxidant activity (**Table 4**) [72].

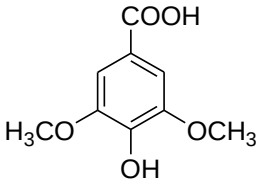
Table 4: Antioxidant profile of vanillic and ferulic acid.

Compound	Free Radical Scavenging Activity (FRSA) (%)		
	0.5 mM	**1.0 mM**	**2.0 mM**
FA	76.02 ± 1.53	91.22 ± 1.27	96.13 ± 0.83
VA	45.31 ± 0.54	50.19 ± 0.67	53.45 ± 1.07
ATP	59.38 ± 0.56	78.06 ± 0.64	84.95 ± 1.44
BHT	70.68 ± 0.50	85.93 ± 0.65	88.51 ± 1.33
DDG	75.59 ± 0.91	92.4 ± 1.32	95.78 ± 0.61

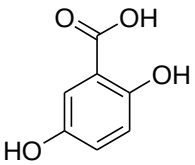
FA = ferulic acid, VA = vanillic acid, ATP = α-tocopherol, BHT = butylated hydroxyl toluene, DDG = dodecyl gallate

Laghari *et al.* carried out a study to evaluate the total free phenolic contents and antioxidant activity of methanolic extracts of leaves and fruits of *Chenopodium album*. Vanillic acid (2) was reported among the phenolic contents of extracts. Antioxidant activity was determined by the DPPH radical scavenging activity. Results revealed that leaves extract gave 83.83% and fruit extract gave 80.55% radical scavenging activity [52].

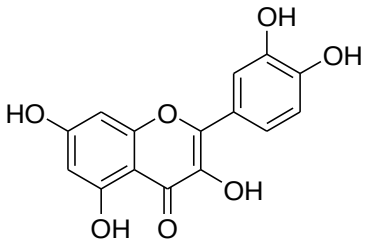
Bhanja *et al*. carried out a study to check the increase in phenolic contents and antioxidant activity of 54% ethanolic extract of wheat after fermentation with two GRAS filamentous fungi namely *Aspergillus oryzae* and *Aspergillus oryzae nakazawa*. Vanillic (2), ferulic (1), caffeic (5), salicylic (14), syringic (11), *p*-coumaric (6), gentisic (15) and sinapic acid (10) were reported as phenolic acid constituents in wheat extract. Antioxidant activity was determined by the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay. Vitamin C equivalent antioxidant capacity (VCEAC) was the unit in which antioxidant activity of the wheat extract was expressed. Increase in the fermentation time caused an increase in 0.834-216.432 µmol/g wheat in case of *Aspergillus oryzae* on 4th day of incubation. DPPH radical scavenging activity of 94.735 µmol VCEAC/g wheat was observed in case of *Aspergillus awamori nakazava* on 5th day of incubation [53].



Salicylic acid
(14)



Gentisic acid
(15)



Querecetin
(16)

Chung *et al.* evaluated the phenolic profile and antioxidant activity of the roots, leaves and fruit of Korean ginseng (*Panax ginseng Meyer*) according to cultivation years (**Table 5**). Phenolic compounds of the Korean ginseng were determined using ultra-high performance liquid chromatography. Salicylic acid (14), *p*-coumaric acid (6), vanillic acid (2), ferulic acid (1), caffeic acid (5), quercetin (16) and vanillin (12) were major phenolics reported. Antioxidant activity was measured by DPPH radical scavenging ability of the ginseng extract. Fruit extract was found most active among all extracts [73].

Table 5: DPPH radical scavenging activity of ginseng fruit, leaf and root extract.

Cultivation year	% Inhibition		
	Fruit	**Leaf**	**Root**
3 yr	89.64 ± 0.64	85.17 ± 0.95	18.08 ± 0.972
4 yr	92.42 ± 0.33	83.52 ± 1.73	19.26 ± 1.14
5 yr	88.28 ± 0.52	84.37 ± 3.10	20.01 ± 2.48
6 yr	91.05 ± 1.79	79.43 ± 8.03	25.61 ± 1.34

Demir *et al.,* carried out a study to evaluate the antioxidant activity and phenolic contents of different species of rose hip (*Rosa* L.) namely *Rosa hirtissma*, *Rosa durmalis subsp. boissieri*, *Rosa gallica*, *Rosa dumalis* and *Rosa cania*.

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

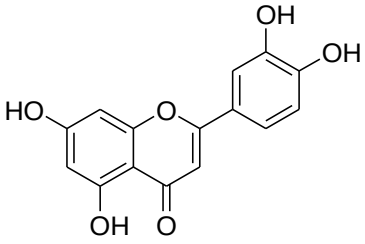
Presence of vanillic acid was found in *Rosa dumalis subsp. boissieri* and *Rosa hirtissma* in concentrations of 10.60 ± 2.31 and 10.83 ± 15.31 µg/gm. Antioxidant activity was determined by three methods namely $ABTS^+$(2,2-azino-di-(3-ethylbenzothialozine-sulphonic acid) method, ferric-reducing antioxidant power (FRAP) assay and DPPH (2,2- diphenyl-1-picrylhydrazyl) radical scavenging method. Extracts of *Rosa hirtissma* species was found as most active antioxidant (**Table 6**) [50].

Table 6: Antioxidant profile of *R. dumalis subsp. boissieri* and *R. hirtissma* species extracts of rose hip

Method used	*R. hirtissma*	*R. dumalis subsp. boissieri*
DPPH (µg/ml)	185.33 ± 16.20	165.01 ± 22.50
FRAP (TE/g)	169.37 ± 0.69	194.36 ± 1.16
$ABTS^+$ (TE/g)	35.53 ± 0.00	35.53 ± 0.01

A study was carried out to determine the antioxidant profile and quality of ginseng seeds after fermentation with different strains namely *Pediococcus*, *lactobacillus* and *Bacillus* strains by Lee *et al*. Phenolic profile reported in extract contained vanillic acid (2), syringic acid (11), ferulic acid (1), gentisic acid (15) and 6 other phenolics. Antioxidant activity was evaluated using 2,2-azine-bis-(3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging activity ($ABTS^+$). The values obtained after fermentation of seeds with *Lactobacillus gasseri* KCTC 3162, *Pediococcus pentosceus* LY011, *Bacillus subtilis* KFRI 1124 and KFRI 1127 were 25.5, 27.09, 31.6 and 32.7% respectively which were relatively higher than control group (15.2%) [49].

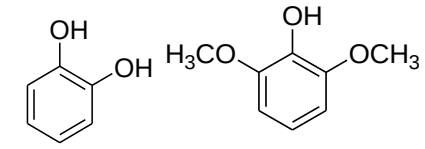
Xiao *et al*. evaluated the antioxidant activity of mung beans which were fermented with *Cordyceps militaris* SN-18. Vanillic acid (2), chlorogenic acid (9), sinapic acid (10) and luteolin (17) were major phenolics reported in mung beans. Antioxidant profile was determined using DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging and ferric-reducing antioxidant power (FRAP) methods. DPPH radical scavenging activity of non-fermented mung beans (NFMB) was found from 601.74 to 1042.06 µg VCE/g (vitamin C equivalents per gram) and that of fermented mung beans (FMB) was from 758.14 to 1469.76 µg VCE/g. FRAP values were found from 5.05 to 9.26 µmol FE(II)/g of NFMB and from 7.09 to 15.97 µmol FE(II)/g [74].



Luteolin
(17)

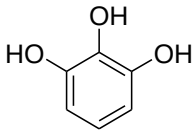
3. **Anticancer activity**

Intisar *et al*. carried out a study to determine the anticancer constituents and cytotoxic activity of methanol-water extract of *Polygonum bistorta* L. (PB). Chief anticancer constituents found were phenolic compounds, including vanillic acid (2), chlorogenic acid (9), gallic acid (7), protocatechuic acid (4), syringic acid (11), *p*-hydroxybenzoic acid (8), catechol (18), syringol (19) and pyrogallol (20). Human hepatocellular carcinoma cell line (HCCLM3) was used to determine the cytotoxic activity of the extract containing phenolic contents. Results revealed that compounds *p*- hydroxybenzoic acid, catechol, pyrogallol, myristic acid were found to possess GI_{50} (50% growth inhibition) values of 86.5 (±3), 92.3 (±3), 118.9 (±3), 107.2 (±3), 126.5 (±3) respectively and possessed cytotoxic activity concentration of 50-400 µg/ml. Hydroquinone, vanillic acid, 4-methyl catechol, syringol, palmitic acid and linoleic acid showed cytotoxic activity at 200-800 µg/ml [59].



Catechol
(18)

Syringol
(19)



Pyrogallol
(20)

Kaliora *et al*. carried out a study to evaluate the phenolic profiles and anticarcinogenic activity of six different Greek herbal infusions named as Rosemary, Cretan dittany, St. John'wort, Sage, Marjoram and Thyme. Vanillic acid (2) in phenolic content of these six infusions was found as 14.8 ± 1.2, 11.2 ± 1.6, 59.0 ± 2.4, 10.6 ± 1.8, 55.7 ± 3.7 µg/200ml respectively. Anti-carcinogenic assay was performed by determining the tendency of all infusions to inhibit the growth of prostate (PC3) and epithelial colon cancer (HT29). From all the infusions checked against HT29 cell growth, the most active infusion found was Cretan dittany with a growth inhibition of 95% at a concentration of 0.6 µg/µL at a time interval of 48 hours. Cretan dittany was also found to be most active against PC3 cells with a growth inhibition of 80% after 24 hours and 90% after 48 hours [60].

Ashraf *et al*. evaluated the chemical composition and antitumor activities of *Eucalyptus camaldulensis* Dehn. leaves extract. Three types of leaf extracts namely methanol, chloroform and hexane were made. Vanillic acid (2) with a concentration of 4.53 ± 0.001 µg/ml was found only in methanol extract. Potato disc assay method was used to determine the antitumor activity of all the extracts. Methanol extract was found to kill 90.09 ± 0.70 % of tumour causing agent (*A. tumefaciens*) with IC_{50} (concentration that showed

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

50% inhibition against tumor) value of 59.68 ± 1.34 µgm/ml [61].

Chatthongpisut *et al*. determined the anti-proliferative ability of Thai purple rice cooked by various methods. Major phenolics found in Thai purple rice were protocatechuic acid and vanillic acid. Cell antiproliferation assay was done on human colon adenocarcinoma cancer cell lines. The highest antiproliferative activity shown by raw rice was at IC_{50} value of 12.63 µg of lyophilized powder/ml. [62].

Anticancer activity of different phenol carboxylic acids obtained from different medicinal herbs was studied by Tao *et al*. Vanillic acid was obtained from plant *Rhizoma Chanxiong.* Anticancer activity of vanillic acid was evaluated by checking COX-2 enzyme inhibition ability. Vanillic acid was found as a good COX-2 enzyme inhibitor with IC_{50} value of 104.7 µM. Celecoxib was used as a positive control [75].

4. **Antidiabetic activity**

Girish *et al*. investigated the phenolic acid composition with their *α-glucosidase* inhibition activity of black gram (*Vigna mungo* L.). Phenolic acid found in significant concentration were gallic, protocatechuic, gentisic, vanillic, syringic, caffeic and ferulic acids. The inhibitory activity of *α-glucosidase* enzyme was performed using the method given by Kwon *et al*., 2008. The seed coat, aleurone layer and plumule fractions of black gram showed 58-70% of enzyme inhibition activity at 2.5 µg. IC_{50} value was found as 1.85, 1.90 and 2.25 µg for the seed coat, plumule and aleurone layer respectively. Germ and whole flour exhibited IC_{50} values of 3.8 and 7 µg respectively. Seed coat fractions, plumule and whole flour extracts were found to possess a good *α-glucosidase* inhibition activity [54].

Wang *et al*. carried out a study to determine the antidiabetic activity of phenolic, triterpenes contents and eleven monomeric compounds of peer's peel and pulp extracts. Activity was checked against *α- glucosidase* inhibition and type-2 diabetic mice. *α- glucosidase* inhibition assay was performed by using the substrate *p*-nitrophenyl- α-D-glucopyranoside (*p*NPG). Inhibition activity was found as approximately 31, 9, 55, 25, 80, 30, 20, 90, 85 and 5% of arbutin, gallic acid, chlorogenic acid, catechin, vanillic acid, epicatechin, *p*-coumaric acid, ferulic acid, rutin and oleanolic acid respectively. In other activity type-2 diabetes was induced in mice by injecting streptozotocin (STZ) which increased the fast blood glucose level (FBG) in mice. After that hypoglycemic potential of extracts of peer's peel and pulp was evaluated by giving a dose of 500 mg/kg daily to the mice (**Table 7**) [55].

Table 7: Effect of pear's peel and pulp extract on FBG in mice (mean ± S.D.)

Group	Blood Glucose Level (mmol/L)			
	Pre-treatment (week)	Post treatment (week)		
	0	1	2	3
Peel (500mg/kg)	13.35 ± 1.77	11.52 ± 2.04	8.64 ± 1.88	8.24 ± 0.57
Pulp (500mg/kg)	13.32 ± 1.63	13.10 ± 2.25	16.05± 4.16	12.44 ± 3.69

Hemalatha *et al*. evaluated the phenolic contents and their-*amylase* inhibition activity of whole and milled fractions of quinoa. Phenolic compounds were analyzed using HPLC. Vanillic and ferulic acid were found as the major phenolics in quinoa.

α-Amylase inhibition assay of phenolic contents of whole grain quinoa was done using the method of Lordan *et al*., 2013. The phenolic extracts showed 49.7%, 70.61%, and 89.53% inhibition at concentrations 108, 162 and 216 µg/ml respectively [56].

Dey *et al*. carried out a study to determine the anti-diabetic activity of leaf extract of plant *Nerium oleander* on alloxan induced diabetes in mice. HPLC analysis at 290 nm reported some of phenolic acids in the extract including vanillic acid , gallic acid and *p*-Coumaric acid. Antidiabetic activity was checked by *α-amylase* inhibition ability of *Nerium oleander* leaf extract (NOLE). Results revealed that 2% inhibition was observed at 200 µg/ml of NOLE having an IC_{50} value of 703.01 ± 56.47 µg/ml [57].

Choi *et al*. evaluated the antidiabetic ability of the several contents from *Euonymus alatus* (EA) twigs. Ferulic acid and vanillic acid were the major phenolic acids reported in EA twigs extract. Antidiabetic profile of the extract was determined by the *α-glucosidase* inhibition assay described by Ademiluyi and Oboh, 2013. Absorbance was taken at 405 nm and acarbose was used as a positive control. The IC_{50} value of vanillic acid was found to be greater than 150 µM [58].

Antidiabetic profile of alcoholic extract of *Aerva lanata* (L.) was studied by Vetrichelvan *et al*. Phytochemical investigations showed the presence of vanillic acid in alcoholic extract of *A. lanata* (AAL). Antidiabetic activity was determined by checking the effect of AAL on diabetic rats. Diabetes in rats was induced by alloxan monohydrate (5% w/v in sterile water). Results showed that a 42% reduction in blood sugar was found at a dose of 375 mg/kg and 48 % at 500 mg/kg body weight of rats by AAL [8].

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

5. Anti-inflammatory activity

Beara *et al*. carried out a study to evaluate the phenolic contents and anti-inflammatory activity of endemic *Plantago reniformis* G. beck. Phenolic contents were determined using LC-MS/MS assay and major phenolics found were vanillic, caffeic, chlorogenic, *p*-hydroxybenzoic and *p*-coumaric acid. Anti-inflammatory activity was determined by the inhibition ability of *Plantago reniformis* extract towards two enzymes namely cyclooxygenase-1 (COX-1) and 12-lipoxygenase (12-LOX). *Plantago reniformis* was found to possess good inhibition activity with IC_{50} values of 3.2 and 5.5 mg/ml towards 12-LOX and COX-1 respectively [65].

Speroni *et al*. carried out a study to determine the anti-inflammatory activity of methanol and butanol extracts of *Balanites aegyptica* bark. The plant was reported to contain vanillic acid, vanillin and N-trans-feruloyltiramine, which were characterized by UV and NMR spectroscopy. Anti-inflammatory activity was investigated by using carrageenan-induced paw edema test. Butanol extract was found to give a dose dependent activity. It showed an inhibition activity of 41 ± 3% and 68 ± 6% at doses 200 mg/kg and 400 mg/kg respectively against the carrageenan-induced edema. On the other hand, methanol extract gave a dose-independent inhibition activity of 28 ± 3% and 32 ± 3% at doses 200 mg/kg and 400 mg/kg respectively [66].

6. Antinociceptive activity

De Los Angeles Yrbas *et al*. carried out a study to determine the antinociceptive activity of vanillic acid. An injection of acetic acid was given to the mice by intraperitoneal route with a dose of 0.1 ml/mg body weight to cause the nociception. Vanillic acid was administered to the mice by intracisternal route (10 and 50 µg/ml) or intraperitoneal route (1-100 mg/kg). Antinociceptive activity was observed by measuring a decrease in the number of abdominal contractions between the control and vanillic acid treated mice groups. Vanillic acid at dose of 100 mg/kg was found to give a highest antinociceptive effect of 88.9% [76].

7. Anti-ulcer activity

Malairajan *et al*. evaluated the antiulcer activity of crude alcoholic extract of *Toona ciliate* Roemer (heart wood). Presence of vanillic acid in heart wood was reported by phytochemical studies. Anti-ulcer activity was checked against three models namely aspirin plus pylorus ligation induced gastric ulcer, water immersion stress induced ulcer and HCl/ethanol induced ulcer in rats. Ranitidine, omeprazole and sucralfate were used as standard drugs in all these models respectively. Results revealed that a dose of 300 mg/kg of the extract showed 100, 43 and 52.94% ulcer inhibition against aspirin plus pylorus ligation, water immersion and HCl/ethanol induced ulcers respectively [34].

CONCLUSION

Vanillic acid is a compound from natural origin and its different types of chemical derivatives were found to possess a wide range of biological activities. From the literature it is reported that vanillic acid and its derivatives consist of mainly antimicrobial, antioxidant, antidiabetic, anticancer, anti-inflammatory, antinociceptive and antiulcer activities. So, vanillic acid is a compound of great interest in medicinal field because of its remarkable properties and also for the research of new medicines for cancer and diabetes like life-threatening diseases.

ACKNOWLEDGEMENT

The authors are thankful to Head, Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, for providing necessary facilities to carry out this work.

AUTHOR'S CONTRIBUTION

Manuscript was prepared, revised and submitted by all the authors.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

The data used in the current study is available from the corresponding author on reasonable request.

FUNDING SOURCE

No external funding source has been disclosed.

REFERENCES

1. Lee H.C., Wei Y.H., Mitochondrial alterations, cellular response to oxidative stress and defective degradation of proteins in aging. Biogerontology. (2001); 2:231-244.
2. Moskovitz L., Yim M.B., Chock P.B., Free radicals and disease. Arch. Biochem. Biophys., (2002); 397:354-359.
3. Halliwell B. Commentary oxidative stress, nutrition and health. Experimental strategies for optimization of nutritional antioxidant intake in humans. Free. Radical. Res. (1996); 25:57-74.
4. Figueroa-Espinoza M.C., Villeneuve P. Phenolic acid lipophilizaton. J. Agric. Food. Chem. 2005; 53:2779-2787.

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

5. Rice-Evans C.A., Miller N.J., Paganga G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free. Radic. Biol. Med., (1996); 20:933-956.
6. Temple N.J., Antioxidants and disease: more questions than answers. Nutr. Res., (2000); 20:449-459.
7. Gavin J.R., et al. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes. Care, 2002; 25, s5-s20.
8. Vetrichelvan T., Jegadeesan M. Anti-diabetic activity of alcoholic extract of Aerva lanata (L.) Juss. ex Schultes in rats. J. Ethnopharmacol., (2002); 80:103-107.
9. Shobana S., Sreerama Y.N., Malleshi N.G. Composition and enzyme inhibitory properties of finger millet (Eleusine coracana L.) seed coat phenolics: Mode of inhibition of α-glucosidase and pancreatic amylase. Food Chem., (2009); 115:1268-1273.
10. Ramasubbu N., Paloth V., Luo Y., Brayer G.D., Levine M.J. Structure of human salivary α-amylase at 1.6 Å resolution: implications for its role in the oral cavity. Acta Crystallographica Section D: Biological Crystallography. (1996); 52:435-446.
11. Bischoff H., Puls W., Krause H.P., Schutt H., Thomas G. Pharmacological properties of the novel glucosidase inhibitors BAY m 1099 (miglitol) and BAY o 1248. Diabetes Research Clin. Pract., (1985); 1, S53.
12. Kim J.S., Hyun T.K., Kim M.J. The inhibitory effects of ethanol extracts from sorghum, foxtail millet and proso millet on α-glucosidase and α-amylase activities. Food Chem., (2011); 124:1647-1651.
13. Mobley H.L., Hausinger R.P. Microbial ureases: significance, regulation, and molecular characterization. Microbiol. Rev., (1989); 53:85-108.
14. Newsholme E., Leech A. Functional biochemistry in health and disease. John. Wiley. Sons., (2011)
15. Yu J.J., Smithson S.L., Thomas P.W., Kirkland T.N., & Cole G.T. Isolation and characterization of the urease gene (URE) from the pathogenic fungus Coccidioides immitis. Gene. (1997); 198:387-391.
16. Pedrozo H.A., Schwartz Z., Luther M., Dean D.D., Boyan B.D., Wiederhold M.L. A mechanism of adaptation to hypergravity in the statocyst of Aplysia californica. Hear. Res., (1996); 102:51-62.
17. Sirko A., & Brodzik R. Plant ureases: roles and regulation. Acta Biochimica Polonica. (1999); 47:1189-1195.
18. Arabski M., Konieczna I., Sołowiej D., Rogon, A, Kolesinska B., Kaminski Z., Kaca W. Are anti-helicobacter pylori urease antibodies involved in atherosclerotic diseases. Clin. Biochem., (2010); 43:115-123.
19. Konieczna I., Zarnowiec P., Kwinkowski M., Kolesinska B., Fraczyk J., Kaminski Z., Kaca W. Bacterial urease and its role in long-lasting human diseases. Curr. Protein. Pept. Sc., (2012); 13:789-806.
20. Dunn B.E., Phadnis S.H. Structure, function and localization of Helicobacter pylori urease. Yale J. Boil. Med., (1998); 71:63.
21. Rozalski A., Kwil I., Torzewska A., Baranowska M., Staczek P. Proteus bacilli: features and virulence factors. Postepy higieny i medycyny doswiadczalnej (Online). (2007); 61:204-219.
22. Wassermann G.E., Olivera Severo D., Uberti A.F., Carlini C.R. Helicobacter pylori urease activates blood platelets through a lipoxygenase mediated pathway. J. Cell. Mol. Med., (2010); 14:2025-2034.
23. Jabbar A., Zaman M.A., Iqbal Z., Yaseen M., Shamim A. Anthelmintic activity of Chenopodium album (L.) and Caesalpinia crista (L.) against trichostrongylid nematodes of sheep. J. Ethnopharmacol., (2007); 114:86-91.
24. Sudina G.F., Mirzoeva O.K., Pushkarevr M.A., Korshunova G., Sumbatyan N.V., Varfolomeev S.D. Caffeic acid phenethyl ester as a lipoxygenase inhibitor with antioxidant properties. FEBS Lett., (1993); 329:21-24.
25. Reddy S., Aggarwal B.B., Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase. FEBS Lett., (1994); 341:19-22.
26. Heleno S.A, Martins A., Queiroz M.J.R., Ferreira I.C., Bioactivity of phenolic acids: Metabolites versus parent compounds: A review. Food. Chem., (2001); 173:501-513.
27. Zhu Y., Li T., Fu X., Abbasi A.M., Zheng B., Liu R.H. Phenolics content, antioxidant and antiproliferative activities of dehulled highland barley (Hordeum vulgare L.). J. Funct. Foods., (2015); 19:439-450.
28. Falleh H., Ksouri R., Chaieb K., Karray-Bouraoui N., Trabelsi N., Boulaaba M., Abdelly C. Phenolic composition of Cynara cardunculus L. organs, and their biological activities. C R. Biol., (2008); 331:372-379.
29. Prince P.S.M., Dhanasekar K., Rajakumar S. Vanillic acid prevents altered ion pumps, ions, inhibits FAS-receptor and caspase mediated apoptosis-signaling pathway and cardiomyocyte death in myocardial infarcted rats. Chem-biol. Int., (2015); 232:68-76.
30. Gawlik-Dziki U., Swieca M., Sułkowski M., Dziki D., Baraniak B., Czyz J. Antioxidant and anticancer activities of Chenopodium quinoa leaves extracts–in vitro study. Food. Chem. Toxicol., (2013); 57:154-160.
31. Mojica L., Meyer A., Berhow M.A., de Mejía E.G. Bean cultivars (Phaseolus vulgaris L.) have similar high antioxidant capacity, in vitro inhibition of α-amylase and α-glucosidase while diverse phenolic composition and concentration. Food. Res. Int., (2015); 69:38-48.
32. Leal L.K., Pierdona T.M., Goes J.G.S., Fonseca K.S., Canuto K.M., Silveira E.R., Viana G.S.B. A comparative chemical and pharmacological study of standardized extracts and vanillic acid from wild and cultivated Amburana cearensis AC Smith. Phytomedicine. (2011); 18:230-233.
33. Dhananjaya B.L., Nataraju A., Rajesh R., Gowda C.R., Sharath B.K., Vishwanath, B.S., D'Souza C.J.

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

Anticoagulant effect of Naja naja venom 5′ nucleotidase: demonstration through the use of novel specific inhibitor, vanillic acid. Toxicon. (2006); 48:411-421.
34. Malairajan P., Gopalakrishnan G., Narasimhan S., Veni K.J.K., Kavimani S. Anti-ulcer activity of crude alcoholic extract of Toona ciliata Roemer (heart wood). J. ethnopharmacol., (2007); 110:348-351.
35. Huang S.M., Hsu C.L., Chuang H.C., Shih P.H., Wu C.H., Yen G.C. Inhibitory effect of vanillic acid on methylglyoxal-mediated glycation in apoptotic Neuro-2A cells. Neurotoxicology., (2008); 29:1016-1022.
36. Kumar S., Prahalathan P., Saravanakumar M., & Raja B. Vanillic acid prevents the deregulation of lipid metabolism, endothelin 1 and up regulation of endothelial nitric oxide synthase in nitric oxide deficient hypertensive rats. Eur. J. Pharmacol., (2014); 743:117-125.
37. Lesage-Meessen L., Delattre M., Haon M., Thibault J.F., Ceccaldi B.C., Brunerie P., Asther M. A two-step bioconversion process for vanillin production from ferulic acid combining Aspergillus niger and Pycnoporus cinnabarinus. J. Biotechnol., (1996); 50: 107-113.
38. Duke J.A. Database of phytochemical constituents of GRAS herbs and other economic plants. CRC Press. (1992).
39. Pacheco-Palencia L.A, Mertens-Talcott S., Talcott S. Chemical composition, antioxidant properties, and thermal stability of a phytochemical enriched oil from Acai (Euterpe oleracea Mart.). J. Agr. Food Chem., (2008); 56:4631-4636.
40. Pearl I.A. Reactions of vanillin and its derived compounds. I. The reaction of vanillin with silver oxide1. J. Am. Chem. Soc., (1946); 68:429-432.
41. Ksouri R., Falleh H., Megdiche W., Trabelsi N., Mhamdi B., Chaieb K., Abdelly C. Antioxidant and antimicrobial activities of the edible medicinal halophyte Tamarix gallica L. and related polyphenolic constituents. Food. Chem. Toxicol., (2009); 47:2083-2091.
42. Dhaouadi K., Meliti W., Dallali S., Belkhir M., Ouerghemmi S., Sebei H., Fattouch S. Commercial Lawsonia inermis L. dried leaves and processed powder: Phytochemical composition, antioxidant, antibacterial, and allelopathic activities. Ind. Crops. Prod., (2015); 77:544-552.
43. Nowacka N., Nowak R., Drozd M., Olech M., Los R., Malm A. Analysis of phenolic constituents, antiradical and antimicrobial activity of edible mushrooms growing wild in Poland. LWT-Food. Sci. Technol., (2014); 59:689-694.
44. Zhao Y., Chen M., Zhao Z., Yu S. The antibiotic activity and mechanisms of sugarcane (Saccharum officinarum L.) bagasse extract against food-borne pathogens. Food Chem., (2015); 185:112-118.
45. Trigui M., Hsouna A.B., Tounsi S., Jaoua S. Chemical composition and evaluation of antioxidant and antimicrobial activities of Tunisian Thymelaea hirsuta with special reference to its mode of action. Ind. Crops Prod., (2013); 41:150-157.
46. Oliveira D.A., Salvador A.A., Smania A., Smania E.F., Maraschin M., Ferreira S.R. Antimicrobial activity and composition profile of grape (Vitis vinifera) pomace extracts obtained by supercritical fluids. J. Biotechnol., (2013); 164:423-432.
47. Naz S., Ahmad S., Rasool S.A., Sayeed S.A., Siddiqi R. Antibacterial activity directed isolation of compounds from Onosma hispidum. Microbiol. Res., (2006); 161:43-48.
48. Razak D.L.A., Rashid N.Y.A., Jamaluddin A., Sharifudin S.A., Long K. Enhancement of phenolic acid content and antioxidant activity of rice bran fermented with Rhizopus oligosporus and Monascus purpureus. Biocatalysis and Agricultural Biotechnology. (2015); 4:33-38.
49. Lee M.H., Lee Y.C., Kim S.S., Hong H.D., Kim K.T. Quality and antioxidant activity of ginseng seed processed by fermentation strains. J. Ginseng. Res., (2015); 39:178-182.
50. Demir N., Yildiz O., Alpaslan M., Hayaloglu A.A. Evaluation of volatiles, phenolic compounds and antioxidant activities of rose hip (Rosa L.) fruits in Turkey. LWT Food Sci. Technol., (2014); 57:126-133.
51. Xiao Y., Zhang Q., Miao J., Rui X., Li T., Dong M. Antioxidant activity and DNA damage protection of mung beans processed by solid state fermentation with Cordyceps militaris SN-18. Innov. Food. Sci. Emerg. Technol. (2015); 31:216-225.
52. Laghari A.H., Memon S., Nelofar A., Khan K.M., Yasmin A. Determination of free phenolic acids and antioxidant activity of methanolic extracts obtained from fruits and leaves of Chenopodium album. Food Chem., (2011); 126:1850-1855.
53. Bhanja T., Kumari A., Banerjee R. Enrichment of phenolics and free radical scavenging property of wheat koji prepared with two filamentous fungi. Bioresour. Technol., (2009); 100:2861-2866.
54. Girish T.K., Pratape V.M., Rao U.P. Nutrient distribution, phenolic acid composition, antioxidant and alpha-glucosidase inhibitory potentials of black gram (Vigna mungo L.) and its milled by-products. Food. Res. Int., (2012); 46:370-377.
55. Wang T., Li X., Zhou B., Li H., Zeng J., Gao W. Anti-diabetic activity in type 2 diabetic mice and α-glucosidase inhibitory, antioxidant and anti-inflammatory potential of chemically profiled pear peel and pulp extracts (Pyrus spp.). J. Funct. Foods. (2015); 13:276-288.
56. Hemalatha P., Bomzan D.P., Rao B.S., Sreerama Y.N. Distribution of phenolic antioxidants in whole and milled fractions of quinoa and their inhibitory effects on α-amylase and α-glucosidase activities. Food. Chem., (2016) 19:330-338.
57. Dey P., Saha M.R., Chowdhuri S.R., Sen A., Sarkar M.P., Haldar B., Chaudhuri T.K. Assessment of anti-diabetic activity of an ethnopharmacological plant Nerium oleander through alloxan induced diabetes in mice. J. Ethnopharmacol., (2015); 161:128-137.

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001

58. Choi C.I., Lee S.R., Kim K.H., Antioxidant and α-glucosidase inhibitory activities of constituents from Euonymus alatus twigs. Ind. Crops. Prod. (2015); 76:1055-106.
59. Intisar A., Zhang L., Luo H., Kiazolu J.B., Zhang R., Zhang W. Anticancer constituents and cytotoxic activity of methanol-water extract of Polygonum bistorta L. Afr. J. Tradit. Complement. Altern. Med., (2012); 10:53-59.
60. Kaliora A.C., Kogiannou D.A., Kefalas P., Papassideri I.S., & Kalogeropoulos N. Phenolic profiles and antioxidant and anticarcinogenic activities of Greek herbal infusions; balancing delight and chemoprevention. Food. Chem., (2014); 142:233-241.
61. Ashraf A., Sarfraz R.A., Mahmood A., Din M. Chemical composition and in vitro antioxidant and antitumor activities of Eucalyptus camaldulensis Dehn leaves. Ind. Crops. Prod., (2015); 74:241-248.
62. Chatthongpisut R., Schwartz S.J., Yongsawatdigul J. Antioxidant activities and antiproliferative activity of Thai purple rice cooked by various methods on human colon cancer cells. Food. Chem., (2015); 188: 99-105.
63. Beara I.N., Lesjak M.M., Cetojevic-Simin D.D., Marjanovic Z.S., Ristic J.D., Mrkonjic Z.O., Mimica-Dukic, N.M. Phenolic profile, antioxidant, anti-inflammatory and cytotoxic activities of black (Tuber aestivum Vittad.) and white (Tuber magnatum Pico) truffles. Food. Chem., (2014); 165:460-466.
64. Hyun T.K., Ko Y.J., Kim E.H., Chung I.M., Kim J.S. Anti-inflammatory activity and phenolic composition of Dendropanax morbifera leaf extracts. Ind. Crops. Prod., (2015); 74:263-270.
65. Beara I.N., Lesjak M.M., Cetojevic-Simin D.D., Orcic D.Z., Jankovic T., Anackov G.T., Mimica-Dukic N.M. Phenolic profile, antioxidant, anti-inflammatory and cytotoxic activities of endemic Plantago reniformis G. Beck. Food Res. Int., (2012); 49:501-50.
66. Speroni E., Cervellati R., Innocenti G., Costa S., Guerra M.C., Dall'Acqua S., Govoni P. Anti-inflammatory, anti-nociceptive and antioxidant activities of Balanites aegyptiaca (L.) Delile. J. Ethnopharmacol., (2005); 98:117-125.
67. Wang X.L., Zhang Y.B., Tang J.F., Yang Y.S., Chen R.Q., Zhang F., Zhu H.L. Design, synthesis and antibacterial activities of vanillic acylhydrazone derivatives as potential β-ketoacyl-acyl carrier protein synthase III (FabH) inhibitors. Eur. J. Med. Chem., (2012); 57:373-382.
68. Cueva C., Moreno-Arribas M.V., Martin-Alvarez P.J., Bills G., Vicente M.F., Basilio A., Bartolome B. Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria. Res. microbiol., (2010); 161:372-382.
69. Aleksic V., Knezevic P. Antimicrobial and antioxidative activity of extracts and essential oils of Myrtus communis L. Microbiol. Res., (2014); 169:240-254.
70. Mourtzinos I., Konteles S., Kalogeropoulos N., Karathanos V.T. Thermal oxidation of vanillin affects its antioxidant and antimicrobial properties. Food Chem., (2009); 114:791-797.
71. Eom T.K., Senevirathne M., Kim S.K. Synthesis of phenolic acid conjugated chitooligosaccharides and evaluation of their antioxidant activity. Environ. Toxicol. Pharmacol., (2012); 34:519-527.
72. Reddy K.K., Ravinder T., Kanjilal S. Synthesis and evaluation of antioxidant and antifungal activities of novel ricinoleate-based lipoconjugates of phenolic acids. Food. Chem. (2012); 134:2201-2207.
73. Chung I.M., Lim J.J., Ahn M.S., Jeong H.N., An T.J., Kim S.H. Comparative phenolic compound profiles and antioxidative activity of the fruit, leaves, and roots of Korean ginseng (Panax ginseng Meyer) according to cultivation years. J. Ginseng. Res., (2016); 40:68-75.
74. Xiao H.H., Gao Q.G., Zhang Y., Wong K.C., Dai Y., Yao X.S, Wong M.S. Vanillic acid exerts oestrogen-like activities in osteoblast-like UMR 106 cells through MAP kinase (MEK/ERK)-mediated ER signaling pathway. J. Steroid Biochem. Mol. Biol., (2014); 144:382-391.
75. Tao L., Wang S., Zhao Y., Sheng X., Wang A., Zheng S., Lu Y. Phenolcarboxylic acids from medicinal herbs exert anticancer effects through disruption of COX-2 activity. Phytomedicine., (2014); 21:1473-1482.
76. De los Angeles Yrbas M., Morucci F., Alonso R., Gorzalczany S. Pharmacological mechanism underlying the antinociceptive activity of vanillic acid. Pharmacol. Biochem. Behav., (2015); 132:88-95.

Indo Global Journal of Pharmaceutical Sciences(ISSN 2249 1023; CODEN- IGJPAI; NLM ID: 101610675) indexed and abstracted in CrossRef (DOI Enabling), CNKI, EMBASE (Elsevier), National Library of Medicine (NLM) Catalog (NCBI), ResearchGate, Publons (Clarivate Analytics), CAS (ACS), Index Copernicus, Google Scholar and many more. For further details, visit http://iglobaljournal.com

Cite this article as: Malik, A.; Khatkar, A.; Kakkar, S. A Review on Pharmacological Activities of Vanillic Acid and its Derivatives. Indo Global J. Pharm. Sci., 2023; 13: 1-12. **DOI**: http://doi.org/10.35652/IGJPS.2023.13001