JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/33085

REVIEW ARTICLE

Tricetin and Tricin: An Overview of the Chemistry, Sources, Contents, and Pharmacological Properties of these Flavones

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Abstract

In this overview, information on the chemistry, sources, contents, and pharmacological properties of two flavones, namely, tricetin (TCT) and tricin (TC), is updated. TCT occurs mainly in honey and pollen of plant species belonging to the genus *Eucalyptus* of the family Myrtaceae. TC is found in monocotyledon species of the family Poaceae, occurring mainly in cereal crops such as oats, barley, rice, wheat, and corn, and in bamboo species. The chemical structure of TCT contains two hydroxyl (OH) groups at C5 and C7 of ring A and three OH groups at C3', C4', and C5' of ring B, with no methoxy (OCH_3) groups. TC has two OH groups at C5 and C7 of ring A, two OCH_3 groups at C3' and C5', and one OH group at C4' of ring B, i.e., at both sides of the C4' OH group. This renders greater bioavailability, higher metabolic stability, and better intestinal absorption to TC than TCT. In this overview, TCT and TC have eight and seven studies on anti-cancer properties, and 14 and 31 studies on other pharmacological properties, respectively. Both flavones are equally strong in terms of cytotoxicity towards cancer cells. With greater bioavailability, higher metabolic stability, and better intestinal absorption, the other pharmacological properties of TC are stronger than TCT, but not for anti-cancer properties.

Keywords: Hydroxylated Flavones, Methoxylated Flavones, Myricetin

Abbreviations: ABCG2 = ATP-binding cassette transporter G2, ABI = anaphase bridging index, AC = acute colitis, AChE = acetylcholinesterase, Akt = protein kinase B, AMPK = adenosine 5'-monophosphate activated protein kinase, AOM = azoxymethane, AP = acute pancreatitis, ATP = adenosine triphosphate, BaP = benzo(a)pyrene, BCRP = breast cancer resistance protein, CCL = CC motif ligand, CDK9 = cyclin-dependent kinase 9, COPD = chronic obstructive pulmonary disease, COX = cyclooxygenase, CXCL11 = C-X-C motif chemokine 11, DR = death receptor, DSS = dextran sulphate sodium, EC_{50} = 50% effective concentration, Egr-1 = early growth response 1, ERK = extracellular signal-regulated kinase, FAK = focal-adhesion-kinase, HCMV = human cytomegalovirus, HEL = human embryonic lung, HIF = heterodimeric transcription factor, HMS = human mesenchymal stem, HO-1, heme oxygenase-1, HS = hepatic stellate, I/R = ischemia/reperfusion, IC_{50} = 50% inhibitory concentration, IL = interleukin, JNK = c-Jun N-terminal kinase, LDL = low-density lipoprotein, LLC = Lewis lung carcinoma, LOX-1 = lectin-like ox-LDL, LPS = lipopolysaccharide, MAPK = mitogen-activated protein kinase, MDI = mixture of 3-isobutyl-1-methylxanthine (M), dexamethasone (D) and insulin (I), MDM = murine double minute, MI = mitotic index, MIC = minimum inhibitory concentration, MMP = matrix metalloproteinase, mTOR = mammalian target of rapamycin, MVT = membrane vascular transport, NF-κB = nuclear factor-kappa B, NO = nitric oxide, Nrf2 = nuclear factor erythroid 2-related factor 2, 6-OHDA = 6-hydroxydopamine, OVA = ovalbumin, PARP = poly (ADP-ribose) polymerase, PBMC = peripheral blood mononuclear cells, PD = Parkinson's disease, PDGF = platelet-derived growth factor, PGE_2 = prostaglandin E_2, PRKCA = protein kinase C alpha, PS = presenilin, RNA = ribonucleic acid, ROS = reactive oxygen species, S1P = sphingosine-1-phosphate, SP = specificity protein, SPHK = sphingosine kinase, SREBP-1 = sterol regulatory element-binding protein 1, T2D = type 2 diabetes, TG = triglyceride, TNF = tumor necrosis factor, UVB = ultraviolet B, and VEGFR = vascular endothelial growth factor receptor.

Article Received on: 21.02.2023 Revised on: 29.11.2023 Accepted on: 01.12.2023

1. Introduction

Flavones are an important class of flavonoids. Found in more than 70 plant families, flavones have been reported in all plant parts including above- and below-ground, and vegetative and reproductive organs[1]. Food sources of flavones are tea leaves, herbs, fruit juice, wine, honey, fruits, vegetables, cereals, and legumes[2].

Flavones (e.g., apigenin and luteolin) have a C6–C3–C6 molecular formula consisting of a three-ring skeleton[3]. They differ from other flavonoids by having a C2–C3 double bond, a a carbonyl group (ketone) at C4 but lack a C3 hydroxyl group at ring C[2-4]. In addition, most flavones have a hydroxyl group at C5 and C7 of ring A and/or C3' and C4' of ring B. Functionally, methylated flavones have better intestinal absorption and metabolic stability than non-methylated flavones[5]. Methylation also enhances their properties such as anticancer, immuno-modulation and antioxidant activities[6,7]. Examples of methylated flavones with one methoxy group are diosmetin, acacetin and chrysoeriol[8,9]. Examples of Polymethylated Flavones (PMFs) with five and six methoxy (OCH_3) groups are tangeretin and nobiletin, respectively[10]. Methylated flavones containing only one or two OCH_3 groups are metabolically more stable and superior in chemo preventive properties than PMF[6].

Besides their functions in plant biochemistry, physiology, and ecology, flavones are important compounds for human health and nutrition. There is increasing scientific evidence for flavones having health-promoting functions such as antioxidant, antibacterial, antiviral, anti-inflammatory, anti-cancer, anti-estrogenic, anti-atherosclerotic, and anti-allergic activities[1,3].

In this overview, the information on the chemistry, sources, contents, and pharmacological properties of two flavones, namely, tricetin and tricin, is updated. Their pharmacological properties are divided into anti-cancer and other pharmacological properties. Data used in the overview are procured from online databases including those of Google, Google Scholar, Science Direct, PubMed, PubMed Central, PubChem, and J-Stage.

2. Chemistry

Tricetin (TCT) or 5,7,3',4',5'-pentahydroxyflavone has a molecular formula of $C_{15}H_{10}O_7$ and a molecular weight of 302.2 g/mol (Figure 1). The aglycone has two hydroxyl (OH) groups at C5 and C7 of ring A, and three OH groups at C3', C4', and C5' of ring B. Ring C is oxygenated at position 1 and has a double bond at C2 to C3 and a carbonyl group (ketone) at C4. The molecular structure of TCT is similar to myricetin except that the latter is a flavonol that bears an OH group at C3. Rings A and B are benzene rings that form the benzoyl system and cinnamoyl system, respectively, while ring C is a heterocyclic system[1]. Together, the three rings form the flavone backbone of TCT.

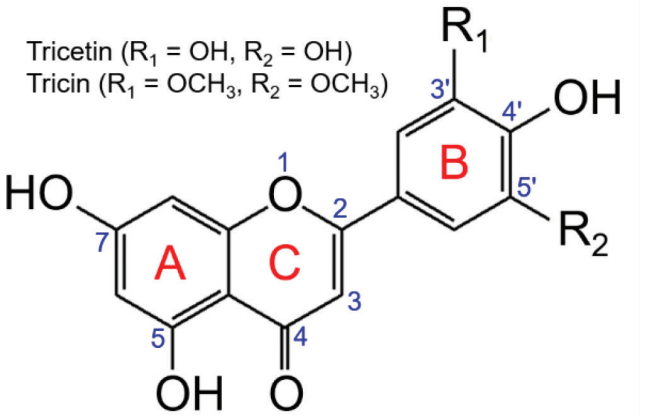

Figure 1. Molecular structure of tricetin and tricin.

Tricin (TC) or 5,7,4'-trihydroxy-3',5'-dimethoxy flavone has a $C_{17}H_{14}O_7$ molecular formula and 330.3 g/mol molecular weight (Figure 1). The aglycone has two hydroxyl groups at C5 and C7 of ring A. There is one OH group at C4', and on both sides are two OCH_3 groups at C3' and C5' of ring B. Similar to TCT, ring C of TC is also oxygenated at position 1, and has a double bond at C2 to C3 and a carbonyl (C=O) group at C4. TC has one OH group at C4' of the B ring and two OCH_3 groups at C3' and C5', i.e., at both sides of the C4' OH group. This renders greater bioavailability, better metabolic stability and higher intestinal absorption to TC[11].

Multiple OH groups in flavonoids confer substantial antioxidant activity, and methoxy groups increase lipophilicity and improve membrane partitioning[12]. A double bond and C=O group increase activity by affording more stable flavonoids. In addition, methylated flavonoids have greater metabolic stability and better permeability to cell membranes during intestinal absorption[5,7]. The structure-activity relationship of PMF

polymethoxylated flavones showed a correlation in the pattern of methoxylation, i.e., the number/position of OCH_3 groups, and anti-proliferative activity towards cancer cells[13,14]. Towards the inhibition of HL60 leukemic cells, an increase in the number of OCH_3 groups at ring A enhanced the activity of PMFs, whereas an increase in OCH_3 groups at ring B reduced activity[14].

3. Sources

TCT occurs in honey and pollen of 27 plant species (Table 1). They belong mostly to species of the genus *Eucalyptus* (11), and the family Myrtaceae (19). Besides honey and pollen, TCT has been reported in the leaf of *Gingko biloba*, the resin of *Heliotropium zeylanicum*, the aerial part of *Inga fendleriana*, the fruit juice of *Morinda citrifolia*, the whole plants of *Potentilla discolour*, flower of *Punica granatum,* and root of *Rhodiola quadrifida*. The foliage of *Eucalyptus crebra* and *Morinda citrifolia* are shown in Figure 2.

TC is found in most monocotyledon species notably the family Poaceae[26]. The aglycone is most commonly reported in cereal crops (bran, hull, husk, grain, lignin, and leaf) such as oats, barley, rice, wheat, and corn (Table 2). It is also found in the leaf of bamboo species that include *Phyllostachys* (2)

Table 1. Plant and product sources of tricetin

S. No.	Species	Common name	Family	Source	References
1	*Banksia ericifolia*	Heath	Myrtaceae	Honey	15
2	*Eucalyptus camaldulensis*	Red river gum	Myrtaceae	Honey	16
3	*E. crebra*	Narrow-leaf ironbark	Myrtaceae	Honey	17
4	*E. globoidia*	Stringybark	Myrtaceae	Honey	17
5	*E. globulus*	Southern blue gum	Myrtaceae	Pollen	18
6	*E. intermedia*	Bloodwood	Myrtaceae	Honey	17
7	*E. largiflorin*	Black box	Myrtaceae	Honey	17
8	*E. melliodora*	Yellow box	Myrtaceae	Honey	16
9	*E. moluccana*	Gum top	Myrtaceae	Honey	17
10	*E. nubila*	Blue top ironbark	Myrtaceae	Honey	17
11	*E. ochrophloia*	Yapunyah	Myrtaceae	Honey	17
12	*E. pilligaensis*	Mallee	Myrtaceae	Honey	16
13	*Ginkgo biloba*	Maiden hair tree	Ginkgoaceae	Leaf	19
14	*Guioa semiglauca*	Crow ash	Myrtaceae	Honey	15
15	*Helianthus annuus*	Sunflower	Asteraceae	Honey	15
16	*Heliotropium zeylanicum*	Heliotrope	Boraginaceae	Resin	20
17	*Inga fendleriana*	Shimbillo	Fabaceae	Aerial part	21
18	*Kunzea ericoides*	White tea tree	Myrtaceae	Pollen	18
19	*Leptospermum scoparium*	Broom tea tree	Myrtaceae	Pollen	18
20	*Lophostemon conferta*	Brush box	Myrtaceae	Honey	15
21	*Melaleuca quinquenervia*	Tea tree	Myrtaceae	Honey	15
22	*Metrosideros excelsa*	NZ Christmas tree	Myrtaceae	Pollen	18
23	*M. umbellata*	Southern Rata	Myrtaceae	Pollen	18
24	*Morinda citrifolia*	Noni	Rubiaceae	Fruit juice	22
25	*Potentilla discolor*	Cinquifoil	Rosaceae	Whole plant	23
26	*Punica granatum*	Pomegranate	Lythraceae	Flower	24
27	*Rhodiola quadrifida*	Rhodiola	Crassulaceae	Root	25

Figure 2. (L–R) *Eucalyptus crebra*, *Morinda citrifolia*, *Avena sativa,* and *Sasa albo-marginata.*

Table 2. Plant and product sources of tricin

S. No.	Species	Common name	Family	Source	References
1	*Agelaea pentagyna*	Agelaea	Connaraceae	Leaf	[27]
2	*Avena sativa*	Oat	Poaceae	Bran	[26]
				Hull	[28]
				Lignin	[29]
3	*Brachypodium distachyon*	Brachypodium	Poaceae	Lignin	[29]
4	*Casearia arborea*	Gia Verde	Salicaceae	Leaf	[30]
5	*Hordeum vulgare*	Barley	Poaceae	Leaf and grain	[26]
6	*Oryza sativa*	Rice	Poaceae	Bran	[31,32]
				Hull and straw	[29]
7	*Phyllostachys glauca*	Bamboo	Poaceae	Leaf	[26]
8	*P. nigra*	Bamboo	Poaceae	Leaf	[26,33]
9	*Sasa albo-marginata*	Bamboo	Poaceae	Leaf	[34-38]
10	*S. borealis*	Bamboo	Poaceae	Leaf	[26]
11	*S. senanensis*	Bamboo	Poaceae	Leaf	[26]
12	*S. veitchii*	Bamboo	Poaceae	Leaf	[26]
13	*Saccharum* sp.	Sugarcane	Poaceae	Bagasse and stem	[29]
14	*Triticum aestivum*	Wheat	Poaceae	Leaf, husk and bran	[26]
15	*T. durum*	Wheat	Poaceae	Straw	[29]
16	*Valeriana laxiflora*	Valerian	Caprifoliaceae	Root	[39]
17	*Zea mays*	Corn	Poaceae	Leaf and stem	[26,29]
18	*Zizania latifolia*	Wild rice	Poaceae	Aerial part	[40,41]

and *Sasa* (4) with *Sasa albo-marginata* most often reported. Cereal crops include the leaf, husk, and bran of wheat (*Triticum aestivum*); leaf and grain of barley (*Hordeum vulgare*); leaf and stem of corn (*Zea mays*); bran, hull, and lignin of oat (*Avena sativa*); and bran, hull, and straw of rice (*Oryza sativa*)[26]. The foliage of *S. albo-marginata* and *A. sativa* are shown in Figure 2.

4. Contents

The content of TCT in *Eucalyptus intermedia* and *E. ochrophloia* honey was 24.6% and 27.4% out of 60.2% and 75.3% of total flavonoids, respectively[17]. The content of myricetin in *E. intermedia* honey was slightly higher at 35.6%. *E. ochrophloia* honey does

not contain myricetin. The total content of flavonoids in *Melaleuca quinquenervia* honey was 6.35 mg/100 g honey with TCT amounting to 1.0 mg/100 g honey[15]. The content of TCT in the ethanol aerial part extract of *Inga fendleriana* was 5.88 µg/mg[21].

Cereal crops have been reported to be a rich source of TC in dry weight. Among the grasses, the highest content of TC (33.1, 32.7, and 28.0 mg/g of lignin) was reported in oats, wheat, and brachypodium, respectively[29]. TC was a major bioactive compound in the ethyl acetate extract of oat hull[28]. Its content was 18 mg/kg, constituting 9.6% of the total phenolic compounds. In Manchurian wild rice, the content of TC ranged from 16.5–25.0 mg/100 g depending on the enzyme treatment and duration of extraction[40]. In different plant parts of winter wheat, the content of TC was the highest in the hull (772 mg/kg) followed by the leaf (253 mg/kg) and the bran (45 mg/kg)[42]. The content of TC in different cereal crops has been quantified to be 23.6, 21.5, and 17.9 µg/g in sprouts of rice, millet, and barley[43], and 1006 and 454 mg/kg in straws of wheat and rice, respectively[44]. A comparison between the TC content in the bran of different rice varieties showed that *Njavara* (1930 mg/kg) has the highest content, followed by *Palakkadan Matta* (120 mg/kg) and Sujatha (48.6 mg/kg)[45].

5. Pharmacological Properties

Recently, the pharmacological properties of TCT against cancer and diabetes have been reviewed[46,47]. Cancers involve breast, lung, and liver cancer, including adenocarcinoma, osteosarcoma and glioblastoma, and diabetes including associated disorders such as inflammation, osteosarcoma, glioblastoma, and atherosclerosis. Bioactivities of TCT involving multi-drug resistance, antioxidant and α-glucosidase inhibition have been briefly mentioned. TC possesses anti-allergy, anti-HIV, anti-inflammatory, antioxidant, antiulcer, anti-viral, anti-diabetic, anti-obesity, anti-tyrosinase, immuno-modulatory, antibacterial, antifungal, anti-histaminic, and anti-tubercular activities[48,49].

5.1 Anti-cancer Activities

TCT inhibited the growth of MCF-7 breast cancer cells with an IC_{50} value of 32.2 µM[50]. Against Hep G2 and PLC/PRF/5 liver cancer cells, IC_{50} values of TCT were 4.87 and 4.23 µM, respectively[51]. Breast, liver, lung, oral, and nasopharyngeal cancer cells including glioblastoma, osteosarcoma, and leukaemia are susceptible to TCT (Table 3).

TC inhibited the proliferation of MDA-MB-468 breast, MCF-7 breast, HT-29 colon, and SW480 colon cancer cells with IC_{50} values of 65.7, 104, 55.2, and 105 µM[31]. Against HBL100 breast and HCEC colon non-cancer cells, inhibition was 77.3 and 84.5 µM, respectively. Inhibition of colony formation by TC towards SW480 colon (16 µM) and MDA-MB-468 breast (0.6 µM) cancer cells was stronger than caffeic acid and protocatechuic acid[31]. Colon, breast, pancreas, prostate, and lung cancer cells including glioma are susceptible to TC (Table 3).

5.2 Other Pharmacological Properties

Other pharmacological properties of TCT include anti-inflammatory, anti-diabetic, poly (ADP-ribose) polymerase (PARP) inhibitory, Breast Cancer Resistance Protein (BCRP) or Adenosine Triphosphate (ATP)-binding cassette transporter G2 (ABCG2) inhibitory, Acetylcholinesterase (AChE) inhibitory, anti-gastric, neuroprotective, lipid inhibitory, and antioxidant activities (Table 4). Anti-inflammatory (5) and anti-diabetic (2) properties represent the major activities of TCT.

Other pharmacological properties of TC include anti-viral, anti-inflammatory, anti-obesity, cyclooxygenase (COX) inhibitory, anti-tubercular, skin photoaging inhibitory, anti-hepatic stellate (HS) cells, anti-tyrosinase, anti-histaminic, anti-angiogenesis, anti-diabetic, anti-leishmanial, osteoblastogenesis, acute colitis amelioration, neuroprotective, immuno-regulatory, c-Jun N-terminal kinase (JNK) inhibitory, and pneumonia attenuation activities (Table 4). Anti-viral (6), anti-inflammatory (5), anti-obesity (4), and cyclooxygenase (COX) inhibitory (2) properties represent the major activities of TCT.

5.3 Structure-activity Relationship

The chemical structure of TC contains two OCH_3 groups at C3' and C5', and one OH group at C4' of ring B, i.e., at both sides of the C4' OH group (Figure 1). TCT has three OH groups at C3', C4', and C5', with no OCH_3 groups. This renders greater bioavailability,

Table 3. Anti-cancer activities of tricetin (TCT) and tricin (TC)

Compound, cancer cell line and cancer type	Effect and mechanism	References
Tricetin		
MCF-7 (breast)	TCT inhibited the growth of cancer cells by inducing cell cycle arrest and apoptosis, convened by activation of caspase-9, inhibition of p53-MDM2, and stabilization of p53.	[50]
HepG2 and PLC/PRF/5 (liver)	TCT induced apoptosis of cancer cells *via* the mitochondrial and DR5 cell death pathways and mediated by ROS generation and JNK activation.	[51]
H460 (lung)	TCT reversed BaP-mediated bone resorption activity of cancer cells by suppressing cancer bone metastasis.	[52]
HSC-3, SCC-9 and OECM-1 (oral)	TCT suppressed the migration of cancer cells by reducing MMP-9 expression and down-regulating the MAPK signalling pathway.	[53]
HONE-1, NPC-39 and NPC-BM (nasopharyngeal)	TCT inhibited the migration of cancer cells by down-regulating PS-1 activity and inhibiting the Akt/GSK-3β pathway.	[54]
GBM 8401 and U87 (glioblastoma)	TCT suppressed the migration and/or invasion of cancer cells by inhibiting MMP-2 *via* the modulation of SP-1 expression and transcriptional activity. When combined with an ERK inhibitor (ERK-DN), a better anti-invasive effect was observed than tricetin treatment alone.	[55]
HOS and U2OS (osteosarcoma)	TCT (up to 80 μM) inhibited the migration and invasion of cancer cells by down-regulation of MMP-9 expression *via* p38 and Akt signalling pathways.	[56]
HL-60 (leukaemia)	TCT induced apoptosis of leukaemia cells through a ROS- and JNK-mediated pathway. The anticancer activity of tricetin was enhanced when combined with an ERK inhibitor.	[57]
Tricin		
Adenocarcinomas (colon)	Dietary administration of mice with TC suppressed AOM/DSS-induced colon carcinogenesis by inhibiting TNF-α in the early phase, and MI and ABI in the later phase.	[58]
HT-29 and Colon26-Luc (colon)	TC inhibited the viability and migration of cancer cells with IC_{50} values of 108 and 34 μM. Inhibition involved the down-regulation of phosphorylated Akt, ERK1/2, and NF-κB, and by significantly suppressing cell motility, respectively.	[43]
MDA-MB-468 (breast)	TC inhibited the growth of cancer cells by cell cycle arrest and not by apoptosis. However, the anti-cancer effect of TC was not reflected in nude mice bearing tumor *in vivo*.	[59]
HepG2 (liver) and IN383/12 (pancreas)	TC was cytotoxic to cancer cells with IC_{50} values of 15 and 7.5 μM, respectively.	[42]
PC3 (prostate)	TC potentiated the effect of docetaxel by significantly decreasing miR-21 in the treatment of cancer cells.	[60]
LLC cells (lung)	TC inhibited the tumor growth primarily by suppressing PRKCA/SPHK/S1P and anti-apoptotic signalling.	[61]
C6 (glioma)	TC inhibited the proliferation and invasion of cancer cells by up-regulation of FAK-targeting microRNA-7 in cancer cells.	[62]

higher metabolic stability, and better intestinal absorption to TC than TCT[11]. In this overview, TCT has eight studies on the anti-cancer and 14 studies on other pharmacological properties, while TC is reflected by seven anti-cancer studies and 31 studies on other pharmacological properties. In terms of cytotoxicity towards cancer cells, it is apparent that TCT is slightly stronger than CT. It appears that the greater bioavailability, higher metabolic stability, and better intestinal absorption of TC than TCT are applicable for other pharmacological but not for anti-cancer properties.

Table 4. Other pharmacological properties of tricetin (TCT) and tricin (TC)

Compound, bioactivity	Description of effect	Reference
Tricetin		
Anti-inflammatory	TCT inhibited PARP-1 nuclear enzyme in pulmonary epithelial cells by 80%. It ranked second to myricetin which displayed 93% inhibition.	63
	TCT displayed anti-inflammatory effects in a mouse model of LPS-induced acute pulmonary inflammation. When compared to those of fisetin, its effects were less pronounced.	64
	TCT protected chondrocytes against IL-1β-induced inflammation in rats by suppressing the MAPK signalling pathway, suggesting its potential use in treating osteoarthritis.	65
	TCT protects vascular endothelial cells from vascular inflammation by inhibiting LOX-1, ERK1/2, and Egr-1, suggesting its potential use in modulating atherosclerosis.	66
	TCT protected acinar cells against AP in mice induced by cerulein. The processes involved the suppression of apoptosis and edema formation in the pancreas, and the reduction of amylase and lipase levels in the serum.	67
Anti-diabetic	TCT displayed stronger α-glucosidase inhibitory activity than acarbose, the anti-diabetic drug. TCT with the greatest number of hydroxyl groups had the strongest α-glucosidase, α-amylase, and lipase inhibitory activities when compared to other flavones.	24
	TCT was able to reverse the poor glucose uptake ability of the hyperglycemic cell model using HepG2 cells induced with high glucose. Metformin used as the positive control, had the strongest anti-diabetic effect on glucose uptake.	68
PARP inhibitory	TCT strongly reduced LPS-induced TNF-α concentration in the blood of COPD patients (−31%) and in IL-6 concentration in the blood of T2D patients (−29%).	69
BCRP/ABCG2 inhibitory	Using the MVT assay, TCT moderately inhibited BCRP/ABCG2 with an IC_{50} value of 0.41µM.	70
AChE inhibitory	Enzyme inhibition based on the Elman assay showed that TCT strongly inhibited AChE with an IC_{50} value of 18.3 µg/ml. Inhibition was stronger than donepezil (22.0 µg/ml) used as the standard.	71
Anti-gastric	TCT strongly inhibited H^+, K^+-ATPase gastric enzyme with an IC_{50} value of 0.31 µM. Inhibition was stronger than myricetin (0.58 µM). Oral administration of TCT (50 mg/kg) exerted significant inhibitory effects on gastric acid secretion in mice.	72
Neuroprotective	A PD model using *Caenorhabditis elegans* showed that TCT protected against neurotoxicity induced by 6-OHDA *via* suppression of the mitochondria-dependent apoptosis pathway and activation of the Nrf2/HO-1 signalling pathway.	73
Lipid inhibitory	Unlike flavonoids such as luteolin, diosmetin, and chrysoeriol which significantly decreased lipid accumulation, TCT up-regulated the levels of intracellular lipids. Assays were done with an MDI mixture.	74
Antioxidant	Among the flavonoids, TCT was a good antioxidant with negligible pro-oxidant activity, unlike myricetin which showed both pro-oxidant and antioxidant effects.	75
Tricin		
Anti-viral	TC significantly suppressed HCMV replication in MRC-5 HEL cells *via* inhibition of COX-2 expression with an EC_{50} value of 0.51 µM.	34
	TC possessed anti-influenza virus properties, ameliorated loss in body weight and improved survival rate in mice infected with the influenza A virus.	35
	TC displayed anti-HCMV effects in MRC-5 HEL cells by inhibiting CXCL11 gene expression.	36
	TC exerted anti-HCMV activity by attenuating the expression of aCCL2 and by inhibiting HCMV virion production.	37
	TC displayed anti-HCMV effects in HEL cells by inhibiting CCL5 induction needed for the growth of the virus.	76

Table 4. Continued...

Compound, bioactivity	Description of effect	Reference
	TC significantly suppressed HCMV replication in HEL fibroblast cells by inhibiting the kinase activity of CDK9.	38
Anti-inflammatory	TC exerted anti-inflammatory effects in LPS-stimulated RAW 264.7 cells by reducing LPS-induced NO, prostaglandin E2, and intracellular ROS production.	77
	TC ameliorated LPS-induced inflammation in human PBMC by modulating MAPK and PI3K/Akt pathways, down-regulating NF-kB signaling, and deactivating COX-2 and TNF-α.	32
	TC exhibited anti-inflammatory effects in LPS-stimulated RAW 264.7 cells *via* activation of AMPK and inhibition of NF-κb.	78
	TC suppressed inflammation-related colon carcinogenesis in mice by significantly inhibiting TNF-α expression in the colon mucosa.	79
	TC (50 μM) exerted anti-inflammatory activity in LPS-activated RAW 264.7 cells by reducing NO production and suppressing the NF-κB pathway.	61
Anti-obesity	TC exhibited anti-adipogenic activity by significantly inhibiting TG accumulation in 3T3-L1 adipocytes without any cytotoxic effects.	28
	TC inhibited adipogenesis and lipogenesis by suppressing fat accumulation in 3T3-L1 pre-adipocytes *via* down-regulation of Akt/mTOR/S6K and Akt/mTORC1/SREBP-1 pathways.	80,81
	TC displayed an anti-obesity effect in obese mice given a high-fat diet by lowering body weight and adipogenesis, and by decreasing serum and hepatic TG levels. The mechanism involved the AMPK pathway.	82
COX inhibitory	TC inhibited COX enzymes and reduced intestinal carcinogenesis in Apc^{Min} mice. In mice on the TC diet, PGE_2 levels in the small intestinal mucosa and blood were reduced by 34% and 40%, respectively.	83
	TC inhibited COX enzymes, with IC_{50} values of 1.0 μM in both HT-29 and HCA-7 colon cancer cells, respectively.	84
Anti-tubercular	TC inhibited *Mycobacterium tuberculosis* with MIC and IC_{50} values of 58.5 and 20.2 μg/ml, respectively.	39
Skin photoaging inhibitory	TC attenuated UVB-induced wrinkle formation in hairless SKH-1 mice by inhibiting the expressions of MMP-1 and MMP-3.	40
Anti-HS cells	TC inhibited the proliferation of cells *in vitro* by blocking tyrosine phosphorylation of the PDGF receptor and signalling pathways, suggesting its potential use in treating hepatic fibrosis.	85
Anti-tyrosinase	TC inhibited tyrosinase activity with an IC_{50} value of 0.27 mg/ml in a non-competitive manner. TC also quenched tyrosinase fluorescence by forming a complex.	86
Anti-histaminic	TC possessed potent anti-histaminic activity against exocytosis from rat leukaemia basophils (IC_{50} value of 4.8 μM). Luteolin and scutellarein ranked second and third with weak inhibition (IC_{50} values of 58 and 67 μM) respectively.	27
Anti-angiogenesis	TC efficiently suppressed tumor angiogenesis *in vitro* by down-regulating both VEGFR2 signalling and HIF-1α activity.	87
Anti-diabetic	TC significantly increased glucose uptake in C2C12 myotubes of glucose-loaded mice by significantly lowering blood glucose levels.	88
Anti-leishmanial	TC exhibited potent inhibitory activity against intra-cellular *Leishmania infantum* amastigotes with an IC_{50} value of 56 μM, suggesting its potential use for treating leishmaniasis.	30
Osteoblastogenesis	TC enhanced osteoblastogenesis in HMS cells *via* the regulation of Wnt/β-catenin signalling.	89
AC amelioration	TC ameliorated AC in mice induced by DSS. TC improved colonic inflammation and modulated harmful microbiota in the gut.	61
Neuroprotective	TC attenuated cerebral I/R injury in nerve cells of male rats by inhibiting autophagy, apoptosis, and inflammation *via* regulation of the PI3K/Akt pathway.	90

Table 4. Continued...

Compound, bioactivity	Description of effect	Reference
Immuno-regulatory	TC suppressed allergic responses in OVA-sensitized mice by reducing the Th2 cytokine level and increasing the Th1 cytokine level, suggesting its potential in treating allergy-related disorders.	41
Pneumonia attenuation	TC attenuated the progression of LPS-induced pneumonia by modulating Akt and MAPK signalling pathways. Against JNK1, its inhibition was 75.4% and 17.7 μM in IC_{50} value.	91,92

6. Conclusion

TCT has been reported mainly in honey and pollen of *Eucalyptus* species while TC is dominant in cereal crops and bamboo species. Both flavones are equally strong in anti-cancer properties but TC has stronger other pharmacological properties than TCT. TC (5,7,4'-trihydroxy-3',5'-dimethoxyflavone) is a methylated flavone with two OCH_3 groups and three OH groups, while TCT (5,7,3',4',5'-pentahydroxyflavone) is a hydroxylated flavone five OH groups and no OCH_3 groups. Studies on the structure-activity relationship of TCT and TC by increasing and decreasing the number of OCH_3 groups, respectively, would be worthy of further investigation.

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