

Table S1. The occurrence of 3', 4', 5, 7-tetramethoxyflavone in natural products.

Plant common name	Scientific name	Form of tetramethoxyflavone	Reference
Knobthorn Acacia	<i>Acacia nigrescens</i>	3', 4', 5, 7-tetramethoxyflavone	Fourie <i>et al.</i> , 1972
Maire's Alstonia	<i>Alstonia mairei</i>	3', 4', 5, 7-tetramethoxyflavone	KNAPSAcK Species-Metabolite Database
Java Tea	<i>Orthosiphon spicatus</i>	3', 4', 5, 7-tetramethoxyflavone	KNAPSAcK Species-Metabolite Database
<i>Redwood</i>	<i>Merrillia caloxylon</i>	3', 4', 5, 7- tetramethoxyflavone	Fraser <i>et al.</i> , 1974
Fingerroot	<i>Boesenbergia pandurata</i>	3', 4', 5, 7- tetramethoxyflavone	KNAPSAcK Species-Metabolite Database
Akane Madder	<i>Rubia akane</i>	3', 4', 5, 7-tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Senecio platyphylloides</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Circassian Milk Vetch	<i>Astragalus circassicus</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Erythrina hypaphorus</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Sphaeria rousseliana</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Fragrant Lip Fern	<i>Cheilanthes fragrans</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Kahikatea	<i>Podocarpus dacrydioides</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Hellebore	<i>Helleborus macranthus</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Rosemary Willow	<i>Salix rosmarinifolia</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Aniba santalodora</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)

	<i>Colchicum filifolium</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Kashmir Iris	<i>Iris kashmiriana</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Velvet Belly Lanternshark	<i>Etmopterus spinax (velvet belly lantern shark)</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Lemonia spectabilis</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Joseph Scale	<i>Matsucoccus josephi</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Centaurea sonchifolia</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Sand Chamomile	<i>Matricaria sabulosa</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Thai Black Ginger	<i>Kaempferia parviflora</i>	3', 4', 5, 7- tetramethoxyflavone	Azuma <i>et al.</i> , 2008, Chaipech <i>et al.</i> , 2012, Lu <i>et al.</i> , 2012 KNApSACk Species-Metabolite Database LOTUS - the natural products occurrence database
Giant Sensitive Plant	<i>Mimosa pigra</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Konjac	<i>Amorphophallus konjac</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Lonchocarpus chiricanus</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Cat's Whiskers	<i>Orthosiphon aristatus</i>	3', 4', 5, 7- tetramethoxyflavone	LOTUS - the natural products occurrence database
	<i>Mucuna holtonii</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Canary Island Pheasant's Eye	<i>Bethencourtia palmensis</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Kumquat	<i>Citrus japonica</i>	3', 4', 5, 7- tetramethoxyflavone	Mizuno <i>et al.</i> , 1991 LOTUS - the natural products occurrence database
Orange Jessamine	<i>Murraya paniculata</i>	3', 4', 5, 7- tetramethoxyflavone	LOTUS - the natural products occurrence database

			KNApSack Species-Metabolite Database Zhang <i>et al.</i> , 2011
Fingerroot	<i>Boesenbergia rotunda</i>	3', 4', 5, 7- tetramethoxyflavone	LOTUS - the natural products occurrence database Tuchinda <i>et al.</i> , 2002 Jaipetch <i>et al.</i> , 1983
Kinokuni Kumquat	<i>Citrus kinokuni</i>	3', 4', 5, 7- tetramethoxyflavone	LOTUS - the natural products occurrence database
Purple Coral Pea	<i>Hardenbergia violacea</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Campanula choziatowskyi</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Beilschmiedia madang</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Pterocaulon serrulatum</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Preussia terricola</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Lavender Sage	<i>Salvia lavanduloides</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Petunia axillaris subsp. parodii</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Heliotropium scabrum</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Stephania dielsiana</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Gentian Sage	<i>Salvia patens</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Chinese Pulsatilla	<i>Pulsatilla chinensis</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Sweetbread	<i>Lactarius mitissimus</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Milkcap			
European Hop- Hornbeam	<i>Ostrya carpinifolia</i> (<i>European hop-hornbeam</i>)	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)

Blue Vervain	<i>Salvia virgata</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Northern Pike	<i>Esox lucius (northern pike)</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Maclura cochinchinensis</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Douglas Fir	<i>Orgyia pseudotsugata</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Tussock Moth	<i>(Douglas fir tussock moth)</i>		
Blackjack Oak	<i>Quercus marilandica</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Mandarin Orange	<i>Citrus reticulata</i>	3', 4', 5, 7- tetramethoxyflavone	KNAPSAcK Species-Metabolite Database LOTUS - the natural products occurrence database
Ginger	<i>Zingiber officinale</i>	3', 4', 5, 7- tetramethoxyflavone	KNAPSAcK Species-Metabolite Database
	<i>Bryobium eriaeoides</i>	3', 4', 5, 7- tetramethoxyflavone	Asamenew <i>et al.</i> , 2019 LOTUS - the natural products occurrence database
	<i>Dialium excelsum</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Blazingstar	<i>Mentzelia decapetala</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Urban's Pitcher Sage	<i>Lepechinia urbanii</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Piper porphyrophyllum</i>	3', 4', 5, 7- tetramethoxyflavone	Rajudin <i>et al.</i> , 2010. LOTUS - the natural products occurrence database
Rough Starthistle	<i>Centaurea scoparia</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
	<i>Fadogia agrestis</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Calamondin	<i>Citrus x aurantium f. deliciosa</i>	3', 4', 5, 7- tetramethoxyflavone	LOTUS - the natural products occurrence database
	<i>Parmotrema nilgherrense</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)

	<i>Thalassiosira weissflogii</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Hound's Tongue	<i>Cynoglossum macrostylum</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Heartleaf	<i>Drymaria cordata</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Drymaria			
Variegated	<i>Aconitum variegatum</i>	3', 4', 5, 7- tetramethoxyflavone	Natural Product Activity and Species Source (NPASS)
Monkshood			
Tangerine	<i>Citrus tangerina</i>	3', 4', 5, 7- tetramethoxyflavone	Kim <i>et al.</i> , 2009
Orange Jessamine	<i>Murraya exotica</i>		Wu <i>et al.</i> , 2018

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Table S2. Chemical-Disease Co-Occurrences that can be prevented by 5,7,3',4'-tetramethoxyflavone.

Decease	<i>In vivo/In vitro</i>	Form of tetramethoxyflavone studied	Mechanism	Reference
inflammatory diseases	<i>In vitro</i> : human mast cells (LAD2)	5,7,3',4'-tetramethoxyflavone	Increases gene expression and release of tumor necrosis factor, C-X-C motif chemokine ligand 8, and vascular endothelial growth factor.	Patel <i>et al.</i> , 2017
allergic and inflammatory conditions.	<i>In vitro</i> : primary human cord blood-derived cultured mast cells	5,7,3',4'-tetramethoxyflavone	Inhibit intracellular calcium level increases and nuclear factor κ B induction	Weng <i>et al.</i> , 2015
inflammatory diseases	<i>In vitro</i> : human mast cells (LAD2) and primary mast cells (hCBMCs)	5,7,3',4'-tetramethoxyflavone	Release of CCL5 and CCL2 and inhibit the activation of p38 α MAPK, JNK, and I κ B- α	Bawazeer <i>et al.</i> , 2019
osteoarthritis	<i>In vivo</i> : OA rat models	5,7,3',4'-tetramethoxyflavone	Inhibiting both EP/cAMP/PKA signaling pathway and β -catenin signaling pathway	Wu <i>et al.</i> , 2014
osteoarthritis	<i>In vitro</i> : C28/I2 cells.	5,7,3',4'-tetramethoxyflavone	Cholesterol dysregulation by increasing the expression of FOXO3a/LXR α /ABCA1 signaling through SIRT1	Peng <i>et al.</i> , (2021)

antiinflammatory	<i>In vivo</i> : mice	3', 4', 7, 8-tetramethoxyflavone	Inhibit synovial human recombinant phospholipase A2 activity, human platelet TXB2 generation, and human neutrophil degranulation.	Ballesteros <i>et al.</i> , 1995
osteoarthritis	<i>In vivo</i> : rats' knee cartilages	3', 4', 7, 8-tetramethoxyflavone	activating the expression of IRE1 α	Wu <i>et al.</i> , 2018
inflammatory diseases	<i>In vitro</i> : human mast cells (LAD2)	3', 4', 7, 8-tetramethoxyflavone	Interaction between neurokinin-1 and ST2 receptors antagonists and siRNA inhibits TNF secretion	Taracanova <i>et al.</i> , 2017
neurodegenerative diseases	<i>In vitro</i> : mast cells and microglia	3', 4', 7, 8-tetramethoxyflavone	Inhibit corticotropin-releasing hormone, neurotensin, and substance P	Theoharides <i>et al.</i> , 2018
allergies, atopic dermatitis, chronic urticaria, cutaneous mastocytosis, and psoriasis	<i>In vivo</i> : mastocytosis or mast cell activation syndrome patients	3', 4', 7, 8-tetramethoxyflavone	Antiallergic and anti-inflammatory actions	Theoharides <i>et al.</i> , 2017
Osteoarthritis	<i>In vivo</i> : osteoarthritis rat models	3', 4', 7, 8-tetramethoxyflavone	Inhibiting both EP/cAMP/PKA signaling pathway and β -catenin signaling pathway	Wu <i>et al.</i> , 2014
Osteoarthritis	<i>In vitro</i> : C28/I2 cells	3', 4', 7, 8-tetramethoxyflavone	Increasing the expression of FOXO3a/LXR α /ABCA1 signaling through SIRT1 and ameliorates cholesterol dysregulation	Peng <i>et al.</i> , 2021
Osteoarthritis	<i>In vivo</i> : rat knee osteoarthritis models	3', 4', 7, 8-tetramethoxyflavone	Up regulating Foxo3a expression and subsequently inhibiting miR-29a/Wnt/ β -catenin signaling activity	Huang <i>et al.</i> , 2019
Osteoarthritis	<i>In vitro</i> : osteoarthritic chondrocytes	3', 4', 7, 8-tetramethoxyflavone	Inhibiting PGE2-induced ERS and GSK-3 β	Yang <i>et al.</i> , 2015
Osteoarthritis	<i>In vitro</i> : chondrocyte	3', 4', 7, 8-	Inhibition of Endoplasmic reticulum stress-induced	Yuan <i>et al.</i> ,

Psoriasis	<i>In vitro</i> : human HaCaT and normal epidermal human keratinocytes	tetramethoxyflavone 3', 4', 7, 8-tetramethoxyflavone	apoptosis with down regulation of GSK-3 β Inhibiting tumor necrosis factor stimulates skin inflammation via mTOR (pmTORSer2448 , pp70S6KThr389 and p4EBP1Thr37/46) signalling.	2017 Patel <i>et al.</i> , 2018
Anti-inflammatory	<i>In vitro</i> : RAW264.7 cells		Inhibited expression of iNOS mRNA and iNOS protein	Sae-Wong <i>et al.</i> , 2011
Amyotrophic lateral sclerosis	<i>In vivo</i> : amyotrophic lateral sclerosis mouse model (TgSOD1 mice)	3', 4', 7, 8-tetramethoxyflavone	Reduced degranulation of mast cells in the tibialis anterior muscle	Theoharides <i>et al.</i> , 2020
Gout	<i>In vitro</i> : xanthine oxidase	3', 4', 7, 8-tetramethoxyflavone	Inhibitory xanthine oxidase	Nakao <i>et al.</i> , 2011
Benign prostate hyperplasia	<i>In vivo</i> : castrated mice	3', 4', 7, 8-tetramethoxyflavone	Suppressed the weights of prostates and seminal vesicles	Murata <i>et al.</i> , 2013

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