

SUPPLEMENTARY MATERIAL

Natural Products and Derivatives as Potential *Zika Virus* Inhibitors: A Comprehensive Review

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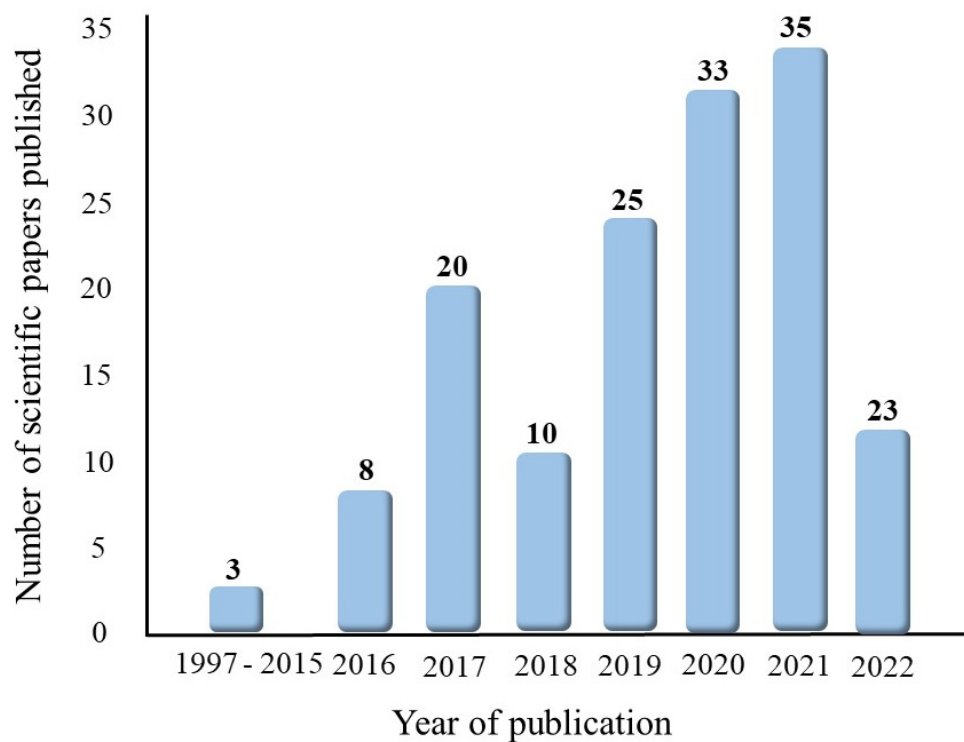


Figure S1: Number of scientific articles reporting natural products tested against ZIKV, published between January 1997 and December 2022. Total of 157 articles.

Table S1. Natural products that interact with molecular targets of ZIKV according to *in silico* data.

<i>Zika virus</i> molecular target	Natural products that interact with the target
MTase domain of NS5	Quercetagenin, Chrysophanic Acid, Jaceidin, Methylglovanon, Caninnot, Luteolin, Quercetin, Redentin, Anthranol, Heliannone B, Hydroxy Kemferol, Secterpathe and Beta Caryophyllene [34]
	Dihydroxy-348-trimethoxy, Isopomiferin, Silydianin B, Amyrisin C, Cannflavin, Derrisin, Mundinol, Schizolaeone B, Tomentodiplacone G, Silydianin, Diprenyleriodictyol, Isosilybin A, Silydin D, Taxifolin,, Silybin C, Silybin B, Silybin A, Lupiwighteone, Euchrenone B, Eryvarin Q, Eryvarin O, Abyssinone V, Sigmoidin C, Sigmoidin B, Robustone, Erycristagallin, (+)-Syringaresinol, Panthenolide, Papraline, Lycopene, Paprarine, Paprairie, Isoach, Fumaritine-N-oxide and Narlumirine [44]
RdRp domain of NS5	Ferulic Acid, 1-Aminocyclopropane-1-carboxylic acid, Cinnamic Acid, Bornylacetate, Salicylic Acid, Cymene, Gamma, Kolin, Fernesene, Myrtenal, Alphaprodine, Beta Pinene, Xylene, Benzaldehyde, Nicotinic Acid, Tridecanoic and Cyclopentadiene [34]
	Amyrisin A, Isopomiferin, Silydianin B, Isomangostin, Mearnsetin, Cannflavin, Derrisin, Mundinol, Schizolaeone B, Tomatidiplacone G, Anthraxin, Diprenyleriodictyol, Isosilybin B, Isosilybin A, Isoerysenegalenseine, Euchrenone B, Eryvarinols A, AbyssinoneV, Sigmoidin C, Sigmoidin B, Robustone, Oxyresveratrol, Osajin, Erycristagallin, Paprarine, Estafin, FumaritineN-oxide, Papracinine and Oxysanguinarine [44]
	Lycorine [63]
	Xanthoangelol [46]
	Polydatin, Dihydrogenistin, Liquiritin, Rhapontin and Cichoriin [48]
Envelope protein domain III	Bacopaside III and bacoside A [51]
	Epicatechin, baicalin, isonimolicinolide, madecassic acid, and apigenin-7- <i>O</i> -beta-D-glucopyranoside [39]
	4-Hydroxy-2-methylacetophenone, Stigmasterol, 6-Octen-1-ol,3,7-dimethyl, megastigmatrienone, myclohexylmethyl hexyl ester and testosterone cypionate [55]
	Palmatine [41]
	Epigallocatechin gallate (EGCG) [53]

	Tanic acid [52]
	Harringtonine [42]
	Chicoric acid, luteone, reserpine, and rosmarinic acid [60]
	Pentagalloylglucose, Parishin A and Stevioside [54]
	Saikosaponin D; Cimicide F; Pomolic acid; Esculentoside A; Esculentoside B; Tinoside 5,7,2',5'-Tetrahydroxy-flavone; Andrographatoside; Cimicifugic acid B1; Cyanidin 3,5-diglucoside; Bruceine F; Delphinidin; Arnicolide D and Kirenol [56]
Capsid protein	Chicoric acid, luteone, reserpine, and rosmarinic acid [60]
Protease	Saikosaponin D; Cimicide F; Methyl euscaphate; Ganoderic acid Y; Pomolic acid; Macrophylloside D; Mudanpioside E; -Chrysanthemin; 8-epi-Loganic acid; Cyanidin 3,5-diglucoside; Arnicolide D; Delphinidin; 6,7-Dehydroartemisinic acid and Cylindrene [56]
Polymerase	Saikosaponin D; Cimicide F; Esculentoside A; Ganoderic acid Y; Methyl euscaphate; Macrophylloside D; Dihydrobrusatol 1; Tinoside; Andrographatoside; Cyanidin 3,5-diglucoside; Delphinidin; Bruceine F; Schizonepetoside A and Nigakilactone K [56]
NS1 protein	Flavonoid-rich fractions (F1 to F10) [60]
	Tangeretin [61]
NS1 e NS3 protein	Bacopaside III and bacoside A [51]
NS2B/NS3, serine protease	Hesperetin (HST) [35]
Helicase	Saikosaponin D; Esculentoside A; Cimicide F; Esculentoside B; Pomolic acid; Benzoyloxypaeniflorin; Macrophylloside D; Chrysanthemin; Mudanpioside E; Tinoside; Cyanidin 3,5-diglucoside; Bruceine F; Delphinidin; Schizonepetoside A and Retinol [56]
NS3 helicase protein	Cassiarina D, 3'-O-metildiplacona, exiguaflavanona A e lactucopicrina [28]
	Baicalein, catechin, muricatetrocin, canthin, eleutheroside B, ellagic acid, epigallocatechin, tneoandrographolide, ponapensin, sangennon [39]
	5,3'-dihydroxy-3,6,7,8,4'-pentamethoxyflavone (5DP); 5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone (5HH); myricetin-3-O-rhamnoside (M3OR) [50]
	Rutin, Nicotiflorin, Isoquercitrin, and Hyperoside [66]
NS2B-NS3 protease	Quecetin [32]
	Flinderol A, flinderol B, angusticornin B, curaridine [28]
	Bromocriptine [29]
	Novobiocin [57]
	Myricetin; Quercetin; Luteolin; Isorhamnetin; Apigenin, Curcumin [31]

	Hydroxychloroquine [30]
	Narigenin [36]
	Quercetin, rutin and pedalitin [38]
	Epigallocatechin gallate, epigallocatechin gallate-7- <i>O</i> -glucopyranoside, epigallocatechin gallate-4'- <i>O</i> - α -glucopyranoside, isoquercetin, rutin, sanggenon O [40]
	Berberine derivatives (4a, 4b, 4c, 4d, 5a, 5b, 5c and 5d) [43]
	Glycyrrhetic acid derivatives 13 and 19 [62]
	Bisandrographolide, Andrographolide, and Andrographiside [45]
	Chicoric acid, luteone, reserpine, and rosmarinic acid [60]
	β -caryophyllene [49]
	Bixin, annatto, crocetin dimethyl ester, ethyl bixin, mycorradicin, norbixin and transcrocetin [47]
NS5 methyltransferase	Cimicifanol, cimicifemato B, ácido rosmarínico, kanzonol Y, curaridina, kanzonol V, solofenol D, (-)-asarina [28]
	Glycyrrhizic acid derivatives conjugated with amino acid (Compound 13 e 14) [62]
	Theaflavin [65]
	Bixin, annatto, crocetin dimethyl ester, ethyl bixin, mycorradicin, norbixin and transcrocetin [47]
NS5 protein	Baicalein and baicalin [37]
	β -caryophyllene [49]
	Tangeretin [61]
NS5 RNA-dependent RNA polymerase	4',7-Digalloylecatechin-di- <i>O</i> -dimethylisoguaiacin, 2,4,4'-trihydroxy-3,3'-diprenylchalcone, flinderol B [28]
	Piperine and Isoscutellarein [64]
	Chicoric acid, luteone, reserpine, and rosmarinic acid [60]
	Rutin, Nicotiflorin, Isoquercitrin, and Hyperoside [66]
Methyltransferase	Sinefungin [58]
	Saikosaponin D; Esculentoside B; Ganoderic acid Y; Methyl euscaphate; Cimicifanol F; Benzoyloxypaeniflorin; Chrysanthemin; Cimicifugic acid B1; Macrophyllolide D; 5,7,2',5'-Tetrahydroxy-flavone; Mudanpioside E; Cyanidin 3,5-diglucoside; Retinol; Bruceine F; Delphinidin and Schizonepetoside A [56]
TNF	Curcumin [33]

Table S2. Anti-ZIKV activity induced by natural products and derivatives, assayed by *in vitro* methods, that showed selectivity index (SI) ≤ 10 .

Source	Sample	Anti-ZIKV activity		Reference
		Cell lineage or Assay model	SI / Biological effect	
Derivatives of quinine	chloroquine	hBMECs cells	SI = 8.21	[90]
Derivatives of quinine	chloroquine	neural stem cells	SI = 7.68	[90]
Bacterium <i>Streptomyces narbonensis</i>	lovastatin	Huh7 cells	SI > 2.5	[173]
Fungus <i>Aspergillus terreus</i>	kitasamycin,	Huh7 cells	SI = > 1.2	[173]
-	(+)- <i>trans</i> -dihydronarciclasine SC, narciclasine SC and pancratistatin SC	Vero C-1008 cells	SI = 7; 4 and 4 respectively	[174]
-	Bromocriptine PC	ZIKV NS2B-NS3 protease inhibition assay Vero cells	IC ₅₀ = 21.6±1.1µM SI > 3.07 Interferes with the steps after the internalization of the ZIKV	[29]
Leaves (L) and Branches (B) (<i>Tontelea micranta</i>)	Hexane EX (L), ethyl acetate (L), methanolic (L), hexane EX (B), chloroform (B) and ethyl acetate (B)	Vero cells	SI = 2.66; 3.03; 4.23; 4.70; 9.60 and 2.85 Virucidal effect, strongly acting on the viral particle, and inhibited the infection at the adsorption and penetration stages, except for the hexane branch extract.	[175]
<i>Tecoma castaneifolia</i> Trunks and leaves	Ethanolic, EX	Vero cells	SI = 1.53 SI > 3.27	[176]
<i>Tecoma garrocha</i> Trunks and leaves	Ethanolic, EX	Vero cells	SI = 1.21 SI > 1.33	[176]
<i>Tecoma stans</i> var. <i>stans</i> Leaves	Ethanolic, EX	Vero cells	SI > 2.03	[176]
<i>Tecoma stans</i> var. <i>angustata</i>	Ethanolic, EX	Vero cells	SI > 3.73	[176]

Leaves				
<i>Tecoma stans</i> var. <i>stans</i> Trunks	Ethyl acetate EX, FR; Aqueous FR and Crenatoside IC	Vero cells	SI = 1.33; SI = 2,53 and SI = 4,25	[176]
<i>Cissus erosa</i> Stems and leaves	Stems ethanolic EX and Leaves ethanolic EX	Vero cells	SI = 8.5 and 3.7 respectively	[177]
<i>Ehretia microphylla</i> ; <i>Combretum indicum</i> ; <i>Psidium guajava</i> ; <i>Clinopodium douglasii</i> ; <i>Blumea balsamifera</i> ; <i>Peperomia pelúcida</i> ; <i>Vitex negundo</i> ; <i>Momordica charantia</i> ; <i>Senna alata</i> and <i>Allium sativum</i>	Aqueous EX	Vero cells	SI = 1.2548; 1.0752; 2.1905; 1.0792; 1.6972; 0.2000; 1.8290; 2.2739; 1.0933 and 1.4160 respectively The authors suggest that the mechanism of viral inhibition is more likely to be via binding with ZIKV viral replication proteins	[56]
Derivatives of flavanone naringenin	7-(hexyloxy)-5- hydroxy-2-(4- hydroxyphenyl)ch roman-4-one; 5-hydroxy-2-(4- hydroxyphenyl)- 7- (octyloxy)chroma n-4-one; 5-hydroxy-2-(4- hydroxyphenyl)- 7- (nonyloxy)chrom an-4-one and 7-(dodecyloxy)-5- hydroxy-2-(4- hydroxyphenyl)ch roman-4-one All compounds are SC	Table S2. <i>Cont.</i> A549 cells	SI = 4.39; 4.12; 4.11 and 4.2 respectively	[178]
<i>Isodon xerophilus</i> Aerial parts	Enanderinanin J IC	A549 cells	SI = 5.6 The autophagy inhibitory activity of enanderinanin J protects host cells from these RNA viruses.	[179]
<i>Ouratea semiserrata</i> Stems	Ethanolic EX, epicatechin PC ,	Vero cells	SI = 1.30, >3.55, > 10.00 and 4.00 respectively	[180]

	catechin PC and rutin PC			
<i>Bruguiera gymnorhiza</i> Fruits and roots	Aqueous EX by maceration	A549 cells	SI = 3.0 and 3.3 respectively Inhibited the infection at the adsorption stage.	[181]
-	Berberine derivatives (4a, 4b, 4c, 5a,5b,5c and 5d)	Vero cells	SI = 4.1, 3.2, 4.7, 7.5, 2.4, 2.6, 2.8 and 2.7 respectively	[43]
-	Lycorine; Pretazettine; Narciclasine; Narciclasine-4-O- β -D-xylopyranoside and 1-acetyl-lycorine	Vero cells Table S2. <i>Cont.</i>	SI = 3.8; 3.8; 6.0; 6.5 and 1.0 respectively	[182]
<i>Angelica keiskei</i>	Xanthoangelol-E	Vero cells	SI = 5	[46]
<i>M. ilicifolia</i> and <i>T. phaeocarpa</i>	-	SH-SY5Y cells	SI=3.4 and SI=4.8 respectively	[83]
<i>Artemisia capilaris</i> and <i>Hedyotis diffusa</i>	Aqueous EX	Vero cells	SI=5.2 and SI=4.9 respectively	[85]
-	Pedalitin and quercetin	Vero cells	SI=4.3 and SI=2.0 respectively	[123]

EC= extract; IC= isolated compound; FR = fraction; CC = Cytotoxic concentration; IC = Inhibitory concentration; EC= effective concentration; SI = selectivity index; PC = purchased compound; SC = synthesized compound; nd = not determined. Vero = kidney epithelial cells of African green monkey; A549 = Human epithelial cells; hBMECs = human brain microvascular endothelial cells

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