内源性小分子酚类物质研究进展及“酚组学”的提出

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摘要: 小分子酚类物质在动植物中广泛存在, 具有一些共同的生物活性。人体内的苯丙氨酸和酪氨酸代谢, 特别是儿茶酚胺类神经递质代谢会产生内源性小分子酚类物质。内源性的小分子酚类物质与人及一些动物的重要生理过程、精神类疾病的发生密切相关, 本文对此做了系统的整理分析。结合课题组前期对天然小分子酚的实验研究和文献分析, 深化了对“小分子酚是一种药理学信号载体”假说的认识, 在此基础上进一步提出“酚组学”的概念, 分析了在“酚组学”的知识框架下将来可以开展的研究方向和研究内容, 为阐释药物作用机制、发现新药物靶点、寻找精神疾病标志物等方面提供了新的研究视角。

关键词: 酚组学; 内源性小分子酚; 天然小分子酚; 精神类疾病; 儿茶酚胺类神经递质

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Research progress on endogenous small-molecule phenolics and the proposal of "phenolomics"

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Abstract: Small-molecule phenolic substances widely exist in animals and plants, and have some shared biological activities. The metabolism of phenylalanine and tyrosine in the human body, and especially the metabolism of catecholamine neurotransmitters, produces endogenous small-molecule phenols. Endogenous small-molecule phenolic substances are functionally related to the important physiological processes and the occurrence of mental diseases in humans and some animals, which are systematically sorts and summarized in this review. Integrating the previous experimental research and literature analysis on natural small-molecule phenols by our research group, the understanding of the hypothesis that "small-molecule phenol are pharmacological signal carriers" was deepened. Based on above, the concept of "phenolomics" was further proposed, analyzed the research direction and research content which can bring into the knowledge framework of phenolomics. The induction of phenolomics will provide wider perspectives on explaining the pharmacological mechanism of drugs, discovering new drug targets, and finding biomarkers of mental diseases.

Key words: phenolomics; endogenous small-molecule phenol; natural small-molecule phenol; psychiatric disease; catecholamine neurotransmitter

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只含C、H、O三种元素的小分子酚类物质 (相对分子质量小于300) 在动植物中广泛存在, 称之为天然小分子酚 (natural small-molecule phenols, NSMPs)[1]。在人及一些动物体内的NSMPs来源有两种, 一种是存在于苯丙氨酸及酪氨酸代谢通路中、主要由儿茶酚胺类神经递质产生的内源性小分子酚 (endogenous small-molecule phenols, ESMPs), 可见于血浆、脑脊液和尿液等体液中。另一种则是外源性的, 包括从食物中直接吸收和转运至体内的外源性小分子酚类物质以及食物经肠道微生物分解后被胃肠道吸收和转运至体内的小分子酚类代谢物[2]。

通过深入的文献挖掘和实验研究发现, NSMPs有一些共通的药理学活性, 如镇静[3,4]、抗焦虑[5,6]、平滑肌松弛[1]等, 称之为酚相 (phenolism); 因此, 酚羟基被认为是一具活性的官能团, 可通过影响神经系统发挥作用[7]。ESMPs作为儿茶酚胺类神经递质的重要小分子代谢物, 它们与神经系统及精神类疾病之间的关系值得更深入的挖掘。为此, 本文对ESMPs的种类及其主要在神经药理活性等方面的研究现状进行综述, 在分析总结的基础上提出“酚组 (phenolome)”及“酚组学 (phenolomics)”的概念, 以便在统一的知识框架下探讨ESMPs的生理、病理学角色及外源性NSMPs的药理学作用。

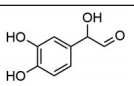
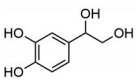
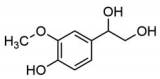
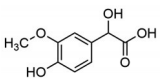
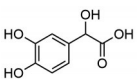
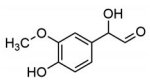
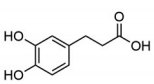
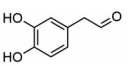
1 ESMPs概述

ESMPs来源主要有儿茶酚胺类神经递质代谢和非儿茶酚胺类神经递质代谢, 其中儿茶酚胺类神经递质代谢中儿茶酚胺包括多巴胺 (dopamine, DA)、去甲肾上腺素 (norepinephrine, NE) 和肾上腺素 (epinephrine, EPI), 吲哚胺主要为5-羟色胺 (5-hydroxytryptamine, 5-HT)。儿茶酚胺类神经递质的前体是芳香族氨基酸产生, 如苯丙氨酸和酪氨酸。苯丙氨酸经苯丙氨酸羟化酶羟基化可形成酪氨酸, 酪氨酸经酪氨酸羟化酶催化生成左旋多巴 (levodopa, *L*-DOPA), 多巴脱羧酶催化*L*-DOPA形成DA, 多巴胺β-羟化酶催化DA形成NE, 最后NE被苯乙醇胺*N*-甲基转移酶和*S*-腺苷蛋氨酸共同作用形成EPI。DA、NE和EPI, 以及苯丙氨酸和酪氨酸在代谢过程中均会产生ESMPs。

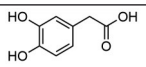
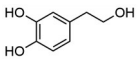
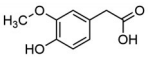
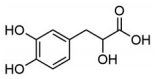
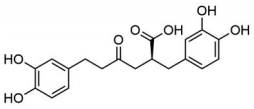
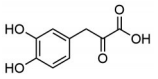
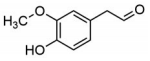
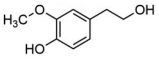
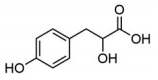
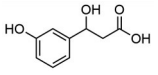
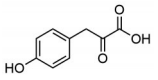
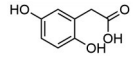
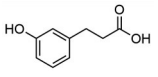
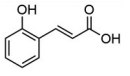
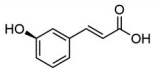
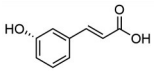
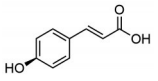
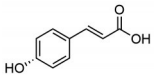
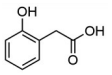
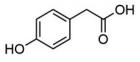
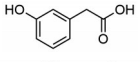
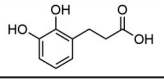
2 ESMPs的种类

利用SciFinder (https://scifinder.cas.org/)、PubChem (https://pubchem. ncbi. nlm. nih. gov/)、KEGG (https://www.genome.jp/kegg/) 和HMDB (https://hmdb.ca/) 数据库, 查询中国知网 (https://www.cnki.net/)、PubMed (https://pubmed. ncbi. nlm. nih. gov/) 和Web of Science (https://www. webofscience. com/wos/woscc/basic-search) 内文献检索ESMPs, 根据所涉及的代谢通路对ESMPs进行分类, 并对文献中这些物质的生物活性进行整理。表1[8-52]展示了苯丙氨酸和酪氨酸代谢通路、NE和DA代谢途径以及一些其他代谢途径产生的具有神经药理活性的ESMPs。

Table 1 Detailed information on endogenous small-molecule phenols (ESMPs). Class 1: Norepinephrine metabolites; Class 2: Dopamine metabolites; Class 3: Phenylalanine metabolites; Class 4: Tyrosine metabolites; Class 5: Other phenolic metabolites

Class	Abbreviation	Name	Structure	Biological activity	Ref.
1	DOPEGAL	3,4-Dihydroxymandelaldehyde		Neurotoxicity	[8]
	DHPG	3,4-Dihydroxyphenylethyleneglycol		Related to psychiatric disorders	–
	MHPG	3-Methoxy-4-hydroxyphenylethyleneglycol		Related to psychiatric disorders	–
	VMA	4-Hydroxy-3-methoxymandelic acid		Related to psychiatric disorders	–
	DOMA	3,4-Dihydroxymandelic acid		Anti-oxidation; toxicity inducers	[9,10]
	MOPEGAL	3-Methoxy-4-hydroxyphenylglycolaldehyde		–	–
2	DHPP	3,4-Dihydroxyphenylpropionic acid		Anti-oxidation; anti-inflammation; neuroprotection	[11,12]
	DOPAL	3,4-Dihydroxyphenylacetaldehyde		Neurotoxicity	[13]

Continued

Class	Abbreviation	Name	Structure	Biological activity	Ref.
	DOPAC	3,4-Dihydroxyphenylacetic acid		Hypotensive; mitochondrial protection; anti-oxidation; anti-inflammation; anti-diabetes; anti-anxiety	[14-17]
	DOPET	3,4-Dihydroxyphenylethanol		Anti-oxidation; neuroprotection	[18,19]
	HVA	3-Methoxy-4-hydroxyphenylacetic acid		Related to psychiatric disorders	−
	DHPLA	3,4-Dihydroxyphenyllactic acid		Anti-oxidation; anti-anxiety; neuroprotection	[20-22]
	ROSA	Rosmarinic acid		Anti-oxidation; anti-inflammation; tissue protection; neuroprotection	[23-26]
	DHPPA	3,4-Dihydroxyphenylpyruvic acid		−	−
	MOPAL	3-Methoxy-4-hydroxyphenylacetaldehyde		−	−
	MHPE	4-Hydroxy-3-methoxyphenylethanol		−	−
3	HDPL	4-Hydroxyphenyllactic acid		Related to psychiatric disorders	−
	HPHA	3-(3-Hydroxyphenyl)-3-hydroxypropanoic acid		Neurotoxicity	[27]
	HPPA	4-Hydroxyphenylpyruvic acid		Related to psychiatric disorders	−
	HGA	2,5-Dihydroxyphenylacetic acid		Endogenous toxins; related to psychiatric disorders	[28]
	HPPT	3-(3-Hydroxyphenyl) propanoic acid		Anti-inflammation; anti-platelet activity; related to psychiatric disorders	[29]
	HCM	2-Hydroxycinnamic acid		Anti-oxidation; related to psychiatric disorders	[30]
	3-HCM	3-Hydroxycinnamic acid		Related to psychiatric disorders	−
	THCM	*trans*-3-Hydroxycinnamic acid		−	−
	PHCA	4-Hydroxycinnamic acid		Anti-oxidation; anti-inflammation; anti-cancer; anti-anxiety; neuroprotection	[31-34]
	PCA	*trans*-4-Hydroxycinnamic acid		−	−
	HPAT	2-Hydroxyphenylacetic acid		Related to psychiatric disorders	−
	HPAA	4-Hydroxyphenylacetic acid		Anti-oxidation; anti-platelet activity; liver protection; anti-anxiety	[35-37]
	3-HPAA	3-Hydroxyphenylacetic acid		Related to psychiatric disorders	−
	2,3-DHHCA	2,3-Dihydroxyphenylpropionic acid		−	−

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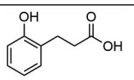
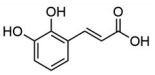
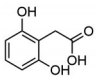
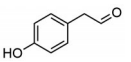
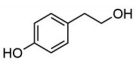
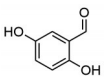
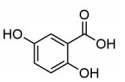
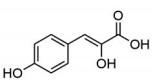
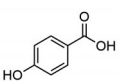
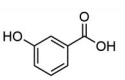
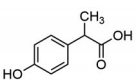
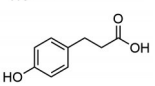
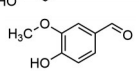
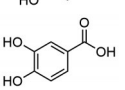
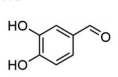
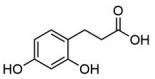
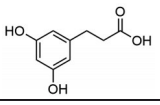
Class	Abbreviation	Name	Structure	Biological activity	Ref.
	3,2-HPHPA	3-(2-Hydroxyphenyl) propanoic acid		–	–
	2,3-DHCCA	2,3-Dihydroxycinnamic acid		–	–
	2,6-DHPL	2,6-Dihydroxyphenylacetate		–	–
4	HPAD	4-Hydroxyphenylacetaldehyde		Related to psychiatric disorders	–
	TYR	4-Hydroxyphenylethanol		Anti-oxidation; anti-inflammation; anti-cancer; neuroprotection	[38-40]
	DHBD	2,5-Dihydroxybenzaldehyde		Related to psychiatric disorders	–
	DHBA	2,5-Dihydroxybenzoic acid		Anti-oxidation; anti-inflammation; anti-bacterial; neuroprotection	[41-43]
	4-HEPPU	4-Hydroxy-enol-phenylpyruvate		–	–
5	HBA	4-Hydroxybenzoic acid		Anti-oxidation; anti-inflammation; neuroprotection	[44,45]
	3-HBA	3-Hydroxybenzoic acid		Anti-oxidation; anti-inflammation; related to psychiatric disorders	[44]
	2,4-HPHPA	2-(4-Hydroxyphenyl) propanoic acid		–	–
	3,4-HPHPA	3-(4-Hydroxyphenyl) propionic acid		–	–
	HMBH	4-Hydroxy-3-methoxybenzaldehyde		Anti-oxidation; anti-inflammation; antibacterial; neuroprotection	[46-48]
	3,4-DHBA	3,4-Dihydroxybenzoic acid		Anti-oxidation; anti-inflammation; liver and kidney protection; neuroprotection	[49-51]
	3,4-DHBAD	3,4-Dihydroxybenzaldehyde		Neuroprotection	[52]
	2,4-DHHCA	2,4-Dihydroxyphenylpropionic acid		–	–
	3,5-DHHCA	3,5-Dihydroxyphenylpropionic acid		–	–

3 ESMPs神经药理活性研究

按照表1中展示的ESMPs的顺序, 此部分主要对儿茶酚胺类神经递质NE代谢 (图1)、DA代谢 (图2), 以及非儿茶酚胺类神经递质代谢 (图3) 产生的ESMPs在神经药理活性方面的研究现状进行整理。

3.1 NE代谢相关的ESMPs

3.1.1 DOPEGAL DOPEGAL是EPI或NE在MAO的作用下生成的代谢物。有研究将DOPEGAL注射到大鼠体内观察EPI能神经元的情况, 发现DOPEGAL可以引起神经元的凋亡和坏死[53]; 在体外DOPEGAL可以激活线粒体内膜导致细胞内Ca^{2+}释放, 从而诱导PC-12细胞的凋亡[54], 说明DOPEGAL在体内和体外均具有神经毒性。DOPEGAL还可能参与如阿尔茨海默症等神经退行性疾病神经元的死亡或细胞的变异, 在中枢神经系统中扮演神经元死亡信使的角色, 发挥内源性神经毒素的作用[8]。此外, 肠应激综合征患者常出现中枢神经系统障碍或焦虑抑郁等症状, 观察到该类患者的尿液中DOPEGAL水平降低, 认为尿液中代

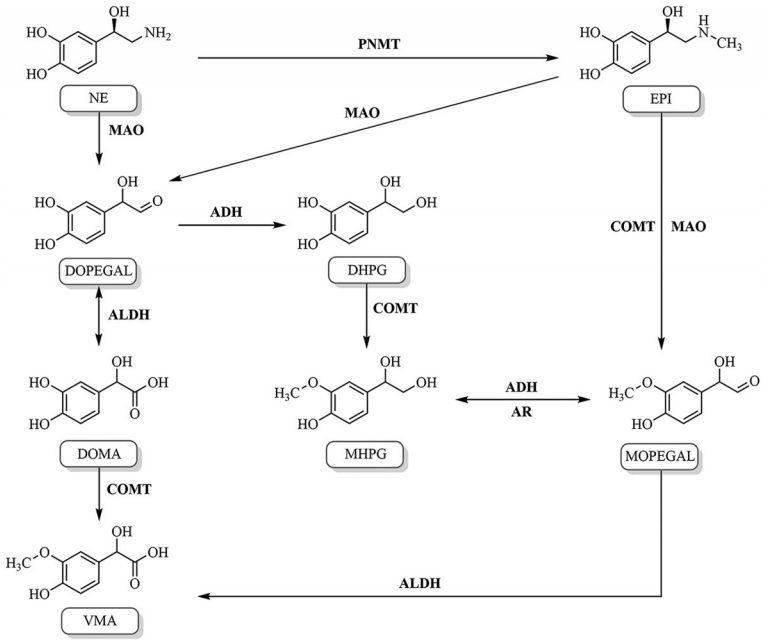


Figure 1 ESMPs produced during the metabolism of norepinephrine (NE). PNMT: Phenylethanolamine N-methyltransferase; MAO: Monoamine oxidase; COMT: Catechol-*O*-methyl transferase; ALDH: Acetaldehyde dehydrogenase; ADH: Alcohol dehydrogenase; AR: Aldose reductase

谢物DOPEGAL水平变化可能与焦虑抑郁状态改变有关[55]。

3.1.2 DHPG与MHPG DHPG可由DOPEGAL在ADH作用下脱氢产生, 之后可以被COMT进一步代谢生成MHPG, 该途径是NE的一条主要代谢途径。DHPG和MHPG存在于人体大脑、血液、脑脊液和尿液中。大脑中DHPG和MHPG是不同的代谢部位中形成的, DHPG主要在突触前和神经元间形成, 而MHPG主要在神经外形成[56]。大脑内游离型的DHPG和MHPG均可以与硫酸根结合形成结合型的硫酸酯类物质, 其结合过程可能与血脑屏障的主动转运机制有关[57]。DHPG和MHPG的变化还与先天性代谢缺陷、认知障碍、中枢神经系统等疾病有关。有研究表明, 抑郁症患者在服药前后血浆中DHPG水平存在变化[58]。目前血浆或脑脊液中DHPG和MHPG水平已被应用于间接评估精神疾病患者的中枢NE能神经元的活动。

3.1.3 VMA VMA是儿茶酚胺类神经递质NE和EPI的终末期代谢物, 也是在尿液中排泄的主要产物。VMA可用于诊断先天性代谢缺陷性疾病, 如酪氨酸血症和苯丙酮尿症, 还可以通过测定尿中排泄量来诊断筛选嗜铬细胞瘤和神经母细胞瘤[59]。Peng等[60]发现给予小鼠小檗碱后可以发挥其抗焦虑作用, 显著降低小鼠的运动情况, 降低脑干中NE和DA的浓度, 增加脑干中VMA和HVA的浓度。Grouzmann等[61]在研究焦虑症患者尿液样本时发现, 尿液中VMA水平与焦虑症之间存在显著的相关性, 提示VMA作为诊断焦虑抑郁等精神类疾病的可能。

3.1.4 DOMA和MOPEGAL DOMA可以由NE脱羧, 或由DOPEGAL在ALDH作用下产生。DOMA可作为一种强大的自由基清除剂和脂质抗氧化剂, 还可以参与中枢神经系统中神经黑色素的生成[9]。MOPEGAL可由NE或EPI在体内代谢产生, 并可以在相关酶的作用下生成MHPG和VMA。但目前关于这两种物质神经药理活性研究的报道较少。

3.2 DA代谢相关的ESMPs

3.2.1 DHPP DHPP又称为二氢咖啡酸, 广泛存在于人体血液和尿液中, 是人类粪便中发现的主要酚酸之一[62]。DHPP可以由*L*-DOPA在DOPARDA的作用下生成。Yingyongnarongkul等[12]发现DHPP对神经细胞具有保护作用。Wang等[7]通过动物模型验证DHPP可以减轻应激诱导的行为, 促进神经可塑性并抑制神经炎症反应。

3.2.2 DOPAL、DOPAC与DOPET DOPAL是DA在MAO催化作用下生成的代谢物, 之后DOPAL会被ALDH代谢生成DOPAC, 或者在次要途径中由AR代谢生成酒精产物DOPET。此外, DOPAL还可以由COMT代谢产生MOPAL。

DOPAL作为DA生成的一种高活性的代谢物, 具有细胞毒性和蛋白质修饰能力, 可能与帕金森病的发病机制有关[63]。Mattammal等[64]发现DOPAL在低至

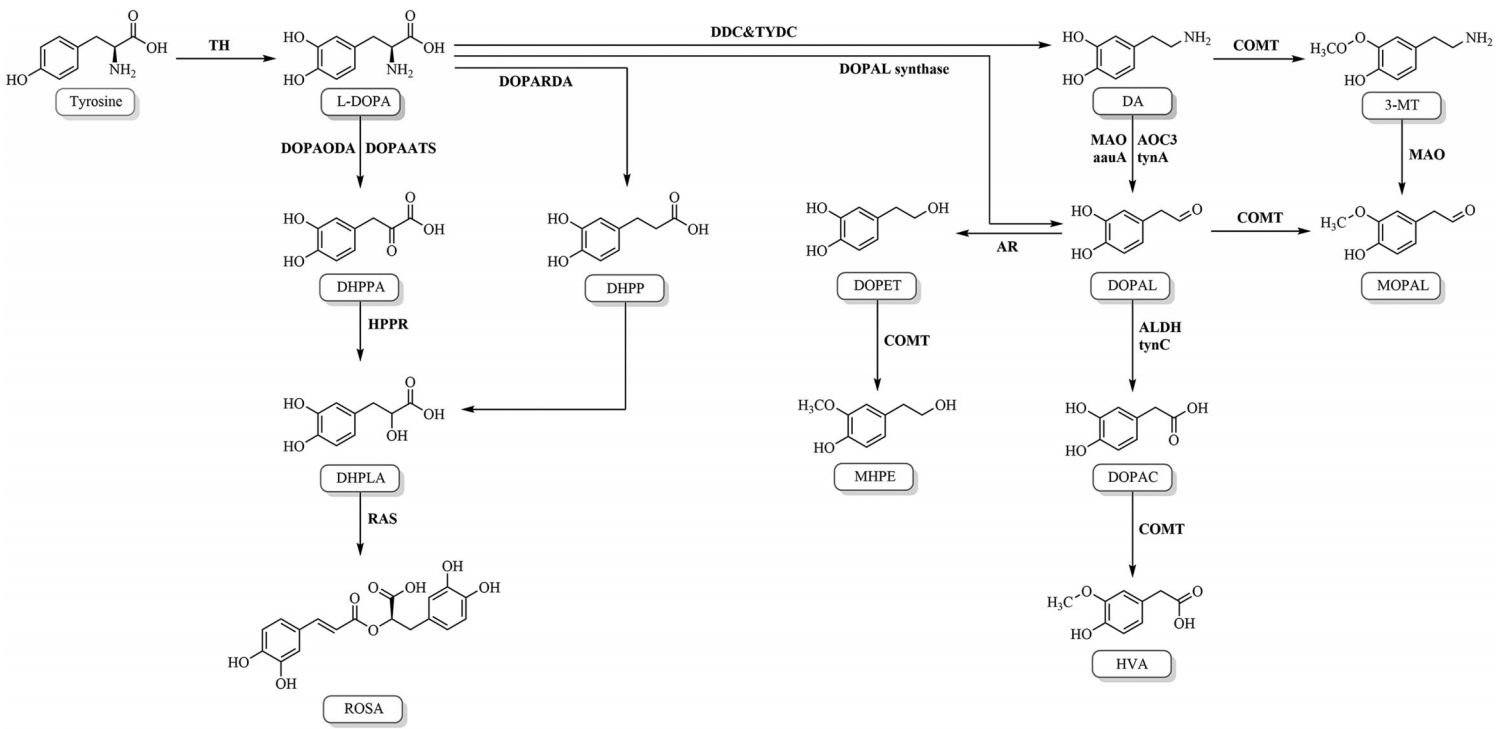


Figure 2 ESMPs produced during the metabolism of dopamine (DA). TH: Tyrosine hydroxylase; DOPARDA: DOPA-reductive deaminase; DOPAODA: DOPA oxidative deaminase; DOPAATS: DOPA aminotransferase; HPPR: Hydroxyphenylpyruvate reductase; DDC: DOPA-decarboxylase; TYDC: Tyrosine decarboxylase; 3-MT: 3-Methoxytyramine; RAS: Rosmarinate synthase; aauA: Aralkylamine dehydrogenase light chain; AOC3: Primary-amine oxidase; tynA: Tyramine oxidase subunit A; AR: Aldose reductase; tynC: Phenylacetaldehyde dehydrogenase

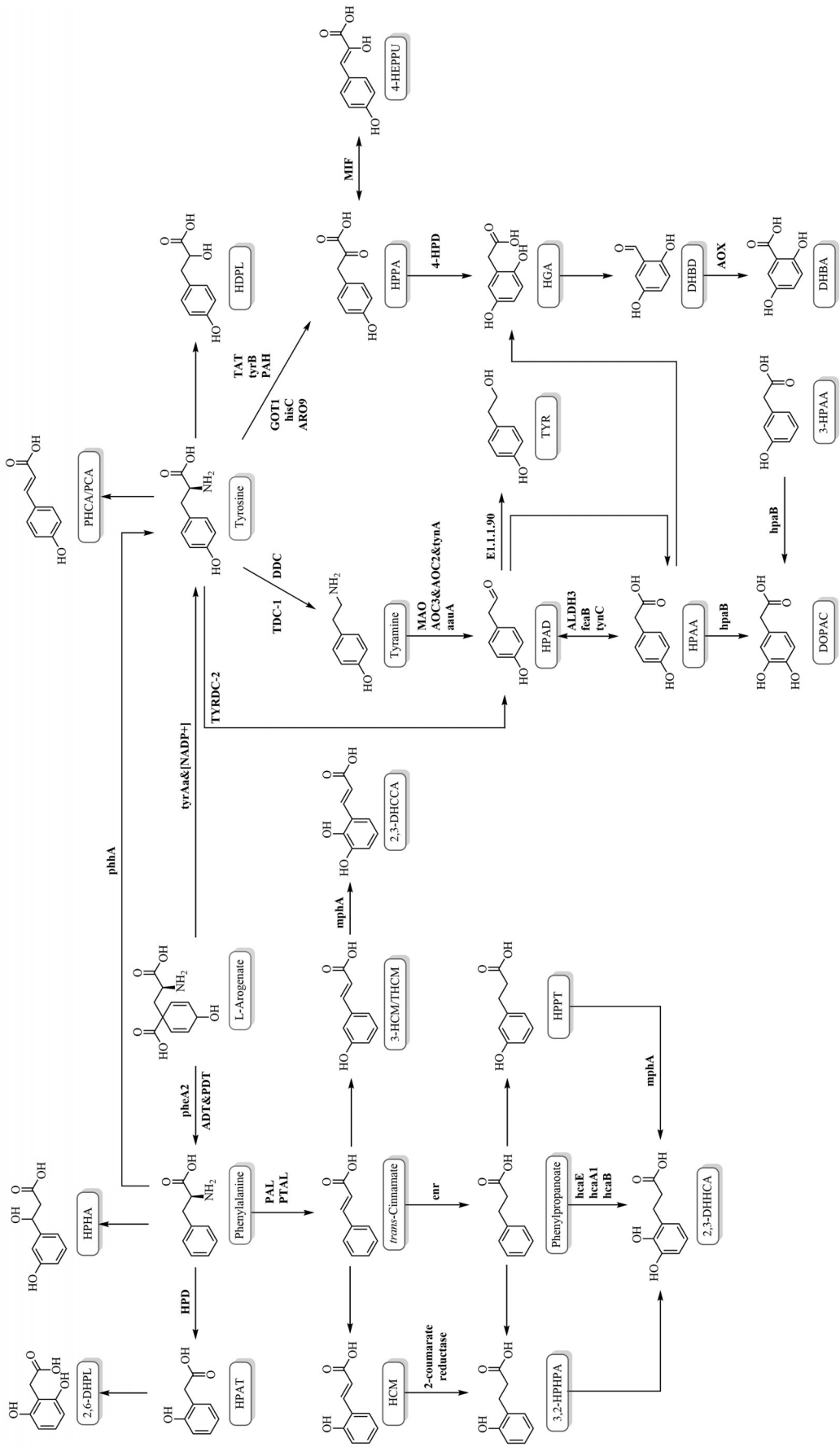


Figure 3　ESMPs produced during the metabolism of phenylalanine and tyrosine. PAL: Phenylalanine ammonia-lyase; PTAL: Phenylalanine/tyrosine ammonia-lyase; enr: 2-Enoate reductase; hcaE: 3-Phenylpropionate; hcaA1: *trans*-Cinnamate dioxygenase subunit alpha; hcaB: 2,3-Dihydroxy-2,3-dihydrophenylpropionate dehydrogenase; mhpA: 3-(3-Hydroxy-phenyl) propionate hydroxylase; tyrAa: Arogenate dehydrogenase; TYRDC-2: 4-Hydroxyphenylacetaldehyde synthase; TDC-1: Tyrosine decarboxylase; AOC2: Primary-amine oxidase; feaB: Phenylacetaldehyde dehydrogenase; hpaB: 4-Hydroxyphenylacetate 3-monooxygenase; TAT: Tyrosine aminotransferase; tyrB: Aromatic-amino-acid transaminase; PAH: Phenylalanine dehydrogenase; GOT1: Aspartate aminotransferase; hisC: Histidinol-phosphate aminotransferase; ARO9: Aromatic amino acid aminotransferase II; HPD: 4-Hydroxyphenylpyruvate dioxygenase; ADT: Arogenate; PDT: Prephenate dehydratase; pheA2: Prephenate dehydratase; phhA: Phenylalanine-4-hydroxylase; AOX: Aldehyde oxidase; MIF: Phenylpyruvate tautomerase

7 μmol·L^{-1}的浓度下对神经细胞具有毒性作用, 推测DOPAL的蓄积可能与神经元功能障碍和DA能神经元的最终丧失有关; DOPAL的醛基还可以与蛋白质的游离伯氨基形成席夫碱, 与神经元蛋白质如α-突触核蛋白结合[65]。Li等[66]发现DOPAL产生的自由基也可能参与了突触核蛋白的氧化修饰和DA能黑质神经元路易小体的形成; 此外, Crawford等[67]发现DOPAL修饰了谷胱甘肽*S*-转移酶, 该酶在抗氧化防御系统中十分重要。以上研究结果均说明DOPAL可在中枢神经系统中作为一种内源性神经毒素或神经元死亡信使, 而且其长期积累或将导致促成DA能神经元的最终死亡[13], 在与神经退行性疾病相关的细胞死亡中发挥重要作用。

DOPAC是脑内神经递质DA的主要内源性代谢物, DOPAC的变化几乎反映了中枢中DA能神经元的功能活动[68]。Zabela等[17]发现DOPAC在大鼠静脉注射给药后表现出抗焦虑活性; Ravenstijn等[69]研究表明, 大脑内纹状体DA和DOPAC水平降低与帕金森氏病和精神分裂症等中枢神经系统疾病有关。

DOPET在体内是由DOPAL在次要代谢途径生成的一种产物, 能够在脑内较好的代谢[70], 外源性DOPET可以在个体内迅速扩散并进入神经元。Tasset等[18]发现DOPET可阻止由3-硝基丙酸引起的纹状体内过氧化脂质的增加和还原型谷胱甘肽水平的降低, 说明DOPET在中枢DA能神经元中也可以发挥其抗氧化能力。Goldstein等[71]认为DOPET可以诱导DA合成的负反馈调节, 抑制TH的产生, 减慢DA的合成速率, 发挥类似增强MAO抑制剂的神经保护作用。

3.2.3 HVA HVA是一种主要的儿茶酚胺代谢终产物。Hwang等[72]利用LC-MS/MS对357例神经母细胞瘤患者尿液样本进行研究, 发现尿液中HVA与神经母细胞瘤之间存在显著的相关性, 可以作为临床大规模诊断和监测神经母细胞瘤患者的生物标志物。Saloner等[73]对102名HIV感染患者的抑郁严重程度和脑脊液中DA能生物标志物的含量进行研究, 结果表明抑郁程度和神经炎症严重的HIV患者脑脊液中的HVA浓度较低。Wang[74]建立焦虑大鼠模型并给予中药酸枣仁, 研究发现与模型组相比给药组大鼠海马组织HVA含量明显升高, Ogawa等[75]对75名抑郁障碍患者的脑脊液中HVA水平进行检测, 得到与前文相同的结果。说明HVA的波动情况可以作为判断焦虑、抑郁等疾病的标志之一。因此, HVA可以作为多种精神类疾病的生物标志物。

3.2.4 DHPLA DHPLA在人体内可以由*L*-DOPA经DOPAODA、DOPAATS和HPPR代谢产生, 在中枢神经系统具有多种药理活性。Kwon等[21]通过动物行为学实验发现, DHPLA可显著抑制MAO-A的活性, 导致中枢神经系统突触间隙DA能神经递质升高, 从而发挥抗焦虑作用。DHPLA还可以减轻帕金森病小鼠的运动功能障碍, 减轻神经炎症, 发挥对DA能神经元的神经保护作用[22], 有望成为防治阿尔茨海默病的有效药物[76]。

3.2.5 ROSA ROSA由咖啡酸与DHPLA酯化形成。ROSA具有抗氧化、抗炎、组织保护等多种生物学活性[23-25], 并在焦虑、抑郁等神经系统疾病中具有神经保护功能[77]。ROSA可以抑制前列腺素、核因子κB (nuclear factor kappa-B, NF-κB)、一氧化氮合酶等促炎细胞因子的合成, 增加或恢复脑源性神经营养因子(brain-derived neurotrophic factor, BDNF) 的水平发挥抗炎和抗氧化作用, 促使突触传递的正常化[77]。Sasaki等[78]发现ROSA的抗抑郁作用与大脑皮层中DA、NE、5-HT和乙酰胆碱等神经递质水平的增加有关。ROSA可以通过增加乙酰胆碱或抑制乙酰胆碱酯酶进而提高神经突触乙酰胆碱的水平[79]; 通过激活γ-氨基丁酸A受体, 减少钙离子内流来抑制谷氨酸的释放发挥神经保护的作用[26]。

3.2.6 DHPPA、MHPE和MOPAL 目前关于神经药理活性研究的报道较少。

3.3 非儿茶酚胺类神经递质代谢相关的ESMPs

非儿茶酚胺类神经递质代谢产生ESMPs的途径主要包括苯丙氨酸代谢通路、酪氨酸代谢通路以及其他代谢通路, 这些ESMPs可以进入人体内血脑屏障, 或改变血脑屏障的通透性, 影响人体的中枢神经系统。

3.3.1 苯丙氨酸代谢通路 苯丙氨酸代谢通路产生的ESMPs包括HDPL、HPHA、HPPA、HGA、HPPT、HCM、3-HCM、THCM、PHCA、PCA、HPAT、HPAA、3-HPAA、2,3-DHHCA、3,2-HPHPA、2,3-DHCCA和2,6-DHPL, 共检索到17种 (表1中Class 3)。

HDPL是一种人体内的苯丙氨酸或酪氨酸代谢产物。Muting等[80]发现HDPL可以影响人体大脑内的新陈代谢。更有研究表明HDPL在苯丙酮尿症和酪氨酸血症患者的脑脊液和尿液中的浓度偏高[81]。Pautova等[82]发现神经外科手术后存在感染或出现炎症的患者, 血清和脑脊液中HDPL的浓度会升高, 并且浓度与病情的严重程度相关。他们认为HDPL可以作为预测和诊断神经外科手术预后或者其他中枢系统感染的一种生物标志物。

HPHA是一种苯丙氨酸代谢物, 在人体尿液中含量丰富[83]。它可以作为一种神经毒素, 破坏儿茶酚胺信号传导, 对神经细胞和神经组织造成损害[27]。

Shaw[27]在研究自闭症和精神分裂症患者的尿液样本时发现患者尿液中HPHA的排泄量增加, 是正常人的300倍左右, 表明长期高水平的HPHA可能与自闭症和精神分裂症有关[84]。同时HPHA的升高也出现在患有抑郁症、癫痫障碍、多动症等疾病的成年人或儿童中, 认为该物质可以作为诊断此类精神类疾病的生物标志物[27]。

HPPA经4-HPD催化可转化为HGA。HGA在人体内积累一定的量将作为肾毒素对人体造成损害, 引发遗传性碱性蛋白尿症[28]。

HPPT是由人体内苯丙氨酸代谢产生, 可以透过人体内血脑屏障, 目前在人体内血清、脑脊液和尿液中被检测到。Shaw[27]和Bouatra等[85]认为尿液中HPPT及其他小分子酚酸增加的排泄量与精神分裂症和自闭症等精神疾病障碍有关。

HCM、3-HCM、THCM、PHCA以及PCA均可由人体内苯丙氨酸代谢产生。Ito等[86]发现3-HCM可以作用于中枢神经系统增加小鼠的自发运动, 并刺激脑内神经引起神经元轴突生长。PHCA可以减少糖尿病大鼠大脑氧化应激, 抑制海马神经病变[87]。此外, 由于PHCA与酪氨酸酶的天然底物*L*-酪氨酸的化学结构十分相似, Kim等[88]发现PHCA是一种有效且具有选择性的人类酪氨酸酶抑制剂, 可以抑制人表皮细胞的黑色素合成。PHCA还具有抗焦虑和神经保护作用, 它可以提高超氧化物歧化酶和过氧化氢酶的活性, 增加神经元环磷酸腺苷 (cyclic adenosine monophosphate, cAMP) 相关的磷酸化, 减轻神经炎症[33,34]。

HPAT主要存在于人体血液、粪便和尿液中, 常在有苯丙酮尿症等疾病的患者的尿液中排泄。HPAA主要由人体内苯丙氨酸产生。Zabela等[37]发现腹腔注射给予小鼠山柰酚后没有观察到它们的行为变化, 而在口服给药后表现出抗焦虑作用, 说明是山柰酚在肠道中的主要代谢物HPAA发挥了抗焦虑活性。目前已有研究将HPAA作为抑郁症的可能生物标志物, 认为其浓度降低与抑郁和焦虑有关[89]; 3-HPAA可能与帕金森病等神经退行性疾病的发生有关[90]。Ho等[91]对肠道微生物代谢产生并且能够穿透血脑屏障的3-HBA、HBA、3,4-DHBA和3-HPAA进行研究, 发现它们可以在体外抑制*α*-突触核蛋白的聚集, 改善*α*-突触核蛋白寡聚体诱导的细胞和神经毒性, 其中3-HPAA可以有效地减弱*α*-突触核蛋白诱导的细胞内聚集。

2,3-DHHCA、3,2-HPHPA、2,3-DHCCA和2,6-DHPL目前关于神经药理活性研究的报道较少。

3.3.2 酪氨酸代谢通路 酪氨酸代谢通路产生的ESMPs包括HPAD、TYR、DHBD、DHBA和4-HEPPU, 共检索到5种 (表1中Class 4)。

HPAD是酪氨酸代谢过程中的关键中间体。TYR又称为酪醇, 在人体内参与酪氨酸代谢, 可以由HPAD代谢产生。TYR也是一种天然酚类化合物, 中药红景天中的主要活性成分红景天苷在体内被广泛代谢以苷元TYR的形式存在。TYR能够减少细胞中活性氧自由基的产生, 减少中枢神经系统中星形胶质细胞释放细胞因子[92], 具有抗炎、抗氧化、神经保护等多种生物学活性。静脉注射TYR可以减少神经功能障碍, 减轻脑组织中的脂质过氧化作用[39]。Khodanovich等[40]研究表明, TYR可以促进正常非增殖性或受损的海马CA1区新神经元的形成和生长, 并对成熟神经元产生神经保护作用。Taniguchi等[93]发现TYR可以作为一种保护神经元免受淀粉样-*β*低聚物神经毒性的天然制剂, 减轻神经元氧化异常和认知障碍。

DHBD和DHBA均参与人体内酪氨酸代谢, 是生物体生长、发育或繁殖所必需的代谢物。其中DHBA在人体内羟基自由基的作用下可以发挥其清除自由基和神经保护能力[43]。

4-HEPPU目前关于神经药理活性研究的报道较少。

3.3.3 其他代谢通路 其他代谢通路产生的ESMPs包括HBA、3-HBA、2, 4-HPHPA、3, 4-HPHPA、HMBH、3,4-DHBA、3,4-DHBAD、2,4-DHHCA和3,5-DHHCA, 共检索到9种 (表1中Class 5)。

HBA、3-HBA、2,4-HPHPA、3,4-HPHPA均能够穿透血脑屏障。其中2,4-HPHPA和3,4-HPHPA常存在于人体血液和尿液中, 是酪氨酸的代谢产物。过氧化氢是神经变性过程中神经细胞死亡的主要原因之一, Winter等[45]发现HBA可以保护大鼠小脑颗粒细胞免受高水平的谷氨酸和过氧化氢的影响, 说明HBA还可以作为一种神经保护剂发挥神经保护和抗神经炎性特性。

HMBH可以在人体内由其他物质代谢产生。HMBH具有良好的渗透性, 可以穿过血脑屏障。Xu等[94]发现HMBH可改善重度抑郁障碍患者的情况。Yan等[95]发现HMBH可以减少体内肿瘤坏死因子-*α*、白细胞介素-6等促炎细胞因子的水平, 通过抑制炎症激活来保护DA能神经元。小胶质细胞是中枢神经系统中具有神经保护功能的巨噬细胞样常驻免疫细胞, 是神经炎症的主要参与者。Kim等[48]通过研究证实HMBH可以抑制脂多糖刺激的小胶质细胞中一氧化氮的产生和促炎细胞因子的表达, 抑制丝裂原活化蛋白激酶和NF-*κ*B的磷酸化, 抑制丝裂原的氧化应激和细胞凋亡。说明HMBH具有抗神经炎症和神经保护

的作用, 可以作为一种天然的抗神经炎性的药物用于治疗神经退行性疾病。

3,4-DHBA 又称为原儿茶酸, 具有抗炎、抗氧化、神经保护[50]等药理活性。Hornedo-Ortega 等[96]发现 3,4-DHBA 可以抑制淀粉样蛋白和 α-突触核蛋白的聚集, 防止聚集后毒性导致的细胞死亡; Kho 等[97]发现给予 3,4-DHBA 后可以显著减少大鼠神经元死亡、小胶质细胞和星形胶质细胞的激活。说明 3,4-DHBA 可用于治疗神经损伤或阿尔茨海默病、帕金森病等神经退行性疾病, 改善学习记忆能力, 恢复认知功能障碍, 促进神经元再生, 在未来可能成为预防神经退行性疾病的有效安全制剂[51]。此外, 3,4-DHBA 还可以调节创伤后应激障碍导致的下丘脑−垂体−肾上腺轴和单胺类物质失调, 抑制了海马区 BDNF 中 mRNA 表达的下降, 显著降低情景恐惧、焦虑和抑郁的行为[98]。3,4-DHBAD 又称为原儿茶醛, 具有抗神经炎症作用。Li 等[52]研究表明 3,4-DHBAD 可以通过抑制小胶质细胞的过度激活, 在脑损伤中发挥神经保护作用。

2,4-DHHCA 和 3,5-DHHCA 目前关于神经药理活性研究的报道较少。

4 总结与展望

通过以上整理分析发现, ESMPs 作为中间产物或代谢终产物参与到重要的生命过程中。例如, 单胺类神经递质的代谢物不但本身会通过反馈抑制调节神经递质的代谢转化, 调节神经功能; 还可能以神经调质或毒素的方式影响神经活动。因此 ESMPs 是一类重要的内源性物质, 与神经生理过程或精神、神经疾病之间存在关联; 在未来或有望成为诊断精神类疾病的潜在生物标志物。又由于一些外源性 NSMPs 在动物上表现出一些共性药理作用, 提示 NSMPs 与 ESMPs 可以共同构成“酚组”, 研究外源性 NSMPs 与 ESMPs 的相互作用可以提供药物开发的新靶点。本文依据代谢组学的原理和思路, 提出“酚组学”的概念, 拟在整体知识框架下对小分子酚类物质进行研究 (图 4)。

“酚组学”是研究生物体内小分子酚类物质时空分布、功能及其代谢调控的科学。通过生理及不同病理状态下小分子酚的代谢及其代谢调控的比较, 了解小分子酚的功能, 识别关键的小分子酚标志物, 从而揭示小分子酚在生命体中的重要作用。基于“酚组学”可以开展以下 (但不限于) 几个方面的研究: ① 建立体内 ESMPs 的检测方法。ESMPs 分子量小, 部分物质的化学性质不稳定, 并且它们在体内含量较低。因此, 在富集样品中 ESMPs 的同时需要保持样品的相对稳定并减少基质在测定过程中的干扰, 提高检测灵敏度和空间分辨率, 优化检测生物样本的时间, 以用于多种类生物样品中 ESMPs 的检测; ② 通过研究疾病状态下 ESMPs 在血液、脑脊液、尿液等体液中的变化规律, 探讨疾病 (特别是精神、神经疾病) 的新标志物或新机制; ③ NSMPs 与 ESMPs 结构极为相似, 通过研究外源性 NSMPs 与机体 ESMPs 的相互作用, 揭示药物作用机制, 如厚朴、灯心草、远志等中药中 NSMPs 的抗焦虑作用等; ④ NSMPs 的摄入能够维持体内平衡并调节整体健康, 降低许多慢性疾病的患病风险[99]。研究通过食物摄入的 NSMPs 的长期作用, 探讨 NSMPs 的保健价值和毒理学意义; ⑤ 探讨小分子酚类物质共通的作用机制, 为开发出更为安全有效的新型精神类疾病药物提供新的研究视角。

作者贡献: 魁宏倩负责文献检索、整理和综述撰写; 刘传鑫负责文章整体思路构建, 对文章进行指导完善; 王强负责文献检索与整理; 黄建梅、翟海峰负责整体学术思路构建, 并

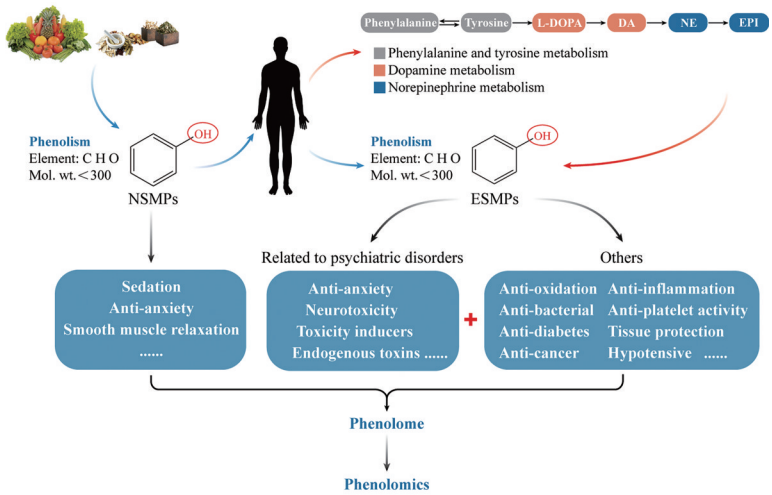


Figure 4 Summary of common pharmacological activities of small-molecule phenols. Mol. wt.: Molecular weight; NSMPs: Natural small-molecule phenols

对文章的写作提供指导性建议并定稿。本文作者共同提出“酚组学”概念。

利益冲突: 所有作者声明本文不存在任何利益冲突。

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