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# 基于血清素通路的功能食品睡眠健康促进作用研究进展

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**摘　要:** 睡眠障碍的发生率逐年升高, 寻找安全有效的干预方式已成为重要研究方向。血清素/5-羟色胺(5-hydroxytryptamin, 5-HT)在睡眠-觉醒调控中发挥核心作用, 其合成、降解及受体信号与昼夜节律密切相关。本文以“5-HT 张力-受体-昼夜节律”框架为主线, 综述了基于 5-HT 通路的功能食品在睡眠健康促进中的研究进展。现有证据表明, 5-HT 对睡眠的作用呈“U 形窗口”: 当张力偏低时易出现入睡困难与高警觉, 当张力过高时则可能导致嗜睡与中枢性疲劳。而适度张力并维持 5-HT1A、5-HT2A 与 5-HT7 受体的平衡及节律同步, 更有利于优化非快速眼动睡眠/快速眼动睡眠(non-rapid eye movement sleep/rapid eye movement sleep, NREM/REM)构成与睡眠连续性。在此基础上, 功能食品的干预路径主要包括 3 方面: (1)通过补充色氨酸及其代谢产物或调控色氨酸羟化酶/单胺氧化酶(tryptophan hydroxylase/monoamine oxidase, TPH/MAO)活性支持合成; (2)通过天然成分的多靶点轻度调节实现受体偏向化作用; (3)通过益生菌、益生元及其代谢物改善肠道微生态并上调 TPH1-5-HT 通路。与此同时, 功能食品在与光照、神经调控或运动等物理手段以及药物干预的联合中, 也展现出协同改善睡眠质量的潜力。未来研究需要在临床试验设计、功能成分标准化、客观与主观终点评价及安全性监测等方面进一步加强, 为基于 5-HT 通路的功能食品研发提供循证支持。

**关键词:** 血清素; 5-羟色胺; 功能食品; 色氨酸; 肠-脑轴; 受体偏向; 进食时相

## Research progress on the role of functional foods targeting the serotonin pathway in promoting sleep health

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**ABSTRACT:** The incidence of sleep disorders is escalating, driving significant research into safe and effective

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interventions. Serotonin/5-hydroxytryptamine (5-HT) plays a central role in sleep-wake regulation; its synthesis, degradation, and receptor signaling are intricately linked to circadian rhythms. This paper reviewed research advances in functional foods that promoted sleep health via the serotonin pathway, centering the discussion on the "5-HT tension-receptor-circadian rhythm" framework. Evidence indicated that 5-HT exerted a U-shaped window effect on sleep: Low levels mought cause difficulty initiating sleep and heightened alertness, whereas excessively high levels could result in daytime sleepiness and central nervous system fatigue. Maintaining a moderate 5-HT tension that synchronized the activity of the 5-HT1A, 5-HT2A and 5-HT7 receptors and optimized the continuity and composition of non-rapid eye movement sleep/rapid eye movement sleep (NREM/REM). Building upon this foundation, the intervention pathways for functional foods primarily encompass 3 aspects: (1) Supporting synthesis through supplementation with tryptophan and its metabolites or by regulating tryptophan hydroxylase/monoamine oxidase (TPH/MAO) activity; (2) achieving receptor bias through multi-target, mild modulation of natural compounds; (3) improving the gut microbiota via probiotics, prebiotics and their metabolites, thereby upregulating the TPH1/5-HT pathway. Furthermore, functional foods demonstrate potential for synergistic improvements in sleep quality when combined with physical interventions (*e.g.*, light therapy, neuromodulation or exercise) and pharmacological treatments. Future research should strengthen areas such as clinical trial design, standardization of functional ingredients, objective and subjective endpoints evaluation, and safety monitoring to provide evidence-based support for the development of functional foods targeting the serotonin pathway.

**KEY WORDS:** serotonin; 5-hydroxytryptamin; functional foods; tryptophan; gut-brain axis; receptor bias; timing of intake

## 0　引　言

睡眠障碍在现代社会日益普遍, 亟需安全、可持续的非药物干预手段。血清素/5-羟色胺(5-hydroxytryptamin, 5-HT)是睡眠-觉醒调控网络中的关键递质, 其在合成与降解过程中受色氨酸羟化酶(tryptophan hydroxylase, TPH)、芳香族氨基酸脱羧酶(aromatic *L*-amino acid decarboxylase, AADC)和单胺氧化酶(monoamine oxidase, MAO)的精细调节; 在信号传导层面, 5-HT1A、5-HT2A 和 5-HT7 等受体与非快速眼动睡眠/快速眼动睡眠(non-rapid eye movement sleep/rapid eye movement sleep, NREM/REM)构成、觉醒维持及昼夜节律密切相关。中枢 TPH2 与外周 TPH1 共同构成互通的 5-HT 系统, 肠道微生物代谢物如短链脂肪酸(short-chain fatty acids, SCFAs)、胆汁酸(bile acid, BA)及微量胺(trace amines, TA)亦可通过上调 TPH1 影响外周 5-HT 合成, 并经迷走-下丘脑-松果体环路作用于中枢节律与睡眠。炎症与应激状态下色氨酸(tryptophan, Trp)分流至犬尿氨酸(kynurenine, KYN)通路则可能削弱 5-HT 合成并损害睡眠结构。

基于此, 本文在整合既往研究的基础上, 围绕"5-HT 张力-受体-节律"构建分析框架, 系统梳理了不同类型功能食品在底物供给与合成支持、受体偏向化调节及肠-脑轴重塑等层面作用于 5-HT 通路的证据, 并结合现有方法学短板与评价指标缺口提出后续研究方向, 期望为睡眠健康功能食品的机制阐释、配方优化和科学评价提供较为集中的参考。需要说明的是, 文中部分中药制剂和化学药物的相关研究, 主要用于阐释 5-HT 通路及其靶点在睡眠调控中的可行性, 本文并不将其界定为功能食品, 而是将其中涉及的食源性成分和作用通路视作功能食品研发的参考。

## 1　5-HT 通路与睡眠调控机制

### 1.1　5-HT 合成与代谢途径

5-HT 的生物合成遵循"两步法": 必需氨基酸 Trp 经 TPH 催化生成 5-羟基-色氨酸(5-hydroxytryptophan, 5-HTP), 继而由 AADC 脱羧生成 5-HT。下游转化方面, 5-HT 可经两条途径生成调控睡眠和昼夜节律的关键激素褪黑激素(melatonin, MT): 其一为 5-HT 先在芳基烷基胺 N-乙酰转移酶(arylamine N-acetyltransferase, AANAT)作用下乙酰化为 N-乙酰血清素(N-acetylserotonin, NAS), 再由 N-乙酰血清素 O-甲基转移酶(N-acetylserotonin O-methyltransferase, ASMT)甲基化生成 MT; 其二是 5-HT 先经儿茶酚-O-甲基转移酶(catechol-O-methyltransferase, COMT)O-甲基化成 5-甲氧基色胺(5-methoxytryptamine, 5-MT), 继而经 AANAT 乙酰化生成 MT。MT 通过其受体 MT1/MT2 参与睡眠调控与昼夜节律同步。

5-HT 的终末清除主要依赖线粒体外膜定位的 MAO, 其中 MAO-A 是 5-HT 氧化脱氨的主要同工酶, 该过程伴随活性氧如过氧化氢的生成, 产物经醛脱氢酶进一步代谢为

5-羟基吲哚乙酸(5-hydroxyindole-3-acetic acid, 5-HIAA)。降低 MAO-A 活性可减少 5-HT 分解，从而提高局部 5-HT 水平[1]。在外周组织，黏膜侧释放的 5-HT 可被肠上皮细胞(intestinal epithelial cell, IEC)的 5-HT 转运蛋白(5-HT transporter/serotonin transporter, SERT)摄取并在胞内经 MAO 代谢清除；循环中的 5-HT 主要由血小板通过 SERT 摄取，并进一步由囊泡转运体加载至致密颗粒(dense granules, DG)中储存，激活时释放参与血管与止血反应[2]。需要强调的是，外周 5-HT 不能直接通过血脑屏障，但可通过“微生物群-肠-脑轴”等神经-内分泌-免疫途径间接影响中枢的睡眠-觉醒网络。5-HT 的主要合成与代谢途径如图 1 所示。

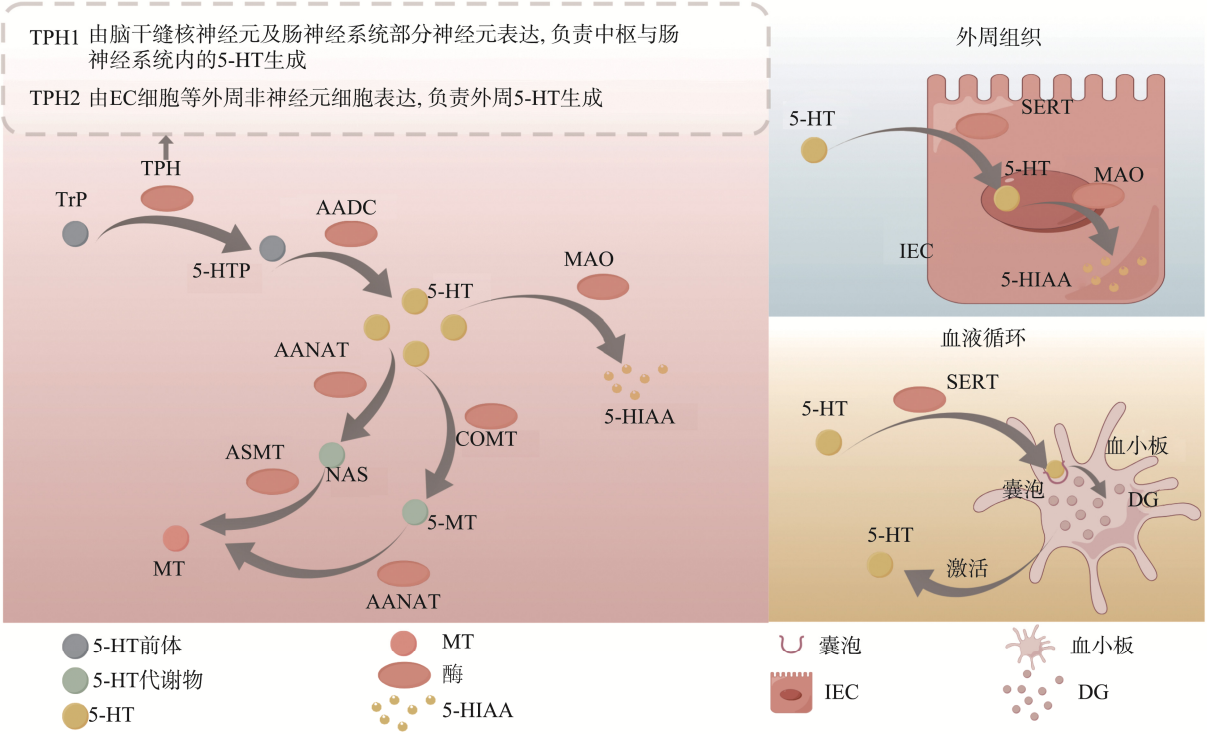



图 1 5-HT 的主要合成与代谢途径

Fig.1 Main synthesis and metabolic pathways of 5-HT

## 1.2 5-HT 在昼夜节律与睡眠-觉醒调控中的作用

### 1.2.1 5-HT 介导的昼夜节律调节

昼夜节律是机体在约 24 h 周期内表现出的生理与行为振荡，用以适应地球自转造成的昼夜更替[3]。哺乳动物的主时钟定位于下丘脑前部的视交叉上核(suprachiasmatic nucleus, SCN)，该核团整合多源输入，包括视网膜下丘脑束(retinohypothalamic tract, RHT)传入的光信号、松果体分泌的 MT，以及中缝核产生的 5-HT 等非光因子[4]。

来自背侧与正中缝核的 5-HT 能投射直接进入 SCN，5-HT 主要通过作用于 SCN 内的 5-HT1A 与 5-HT7 受体调节神经活动，从而影响昼夜节律的周期与相位重设能力[5]。作为 5-HT 的下游代谢产物，MT 与其受体 MT1 结合可降低 SCN 神经元放电频率，进一步参与节律同步与稳定[6]。此外，光信号是最强的外部时间线索，经 RHT 将视网膜信号传递至 SCN，而 5-HT 能神经元能够抑制视网膜到 SCN 的光信号传递，从而控制睡眠-觉醒系统、参与合成褪黑激素以及情绪调节等来影响昼夜节律，同时还能够通过 5-HT1B 受体抑制视网膜神经节细胞释放谷氨酸，从而削弱光信号对 SCN 的相位重设效应[7]。

综上，5-HT 通过 3 条互补机制维持昼夜节律的稳定：(1)直接调控 SCN 神经元受体活性与兴奋性；(2)与 MT 信号通路协同参与相位同步；(3)通过调节光信号传入强度实现节律相位的动态重设。

### 1.2.2 5-HT 对睡眠-觉醒周期的影响

睡眠约占生命全程的三分之一，其有序发生依赖中枢神经系统主导、外周多系统协同的网络调控。5-HT 是最早被证实与睡眠-觉醒密切相关的神经递质之一，在觉醒与入睡的动态转换中发挥关键作用[8−9]。觉醒期，5-HT 神经元高度活跃，释放 5-HT 通过激活 5-HT2A 受体增强大脑皮层的兴奋性与感觉-认知增益，有助于维持清醒状态；进入入睡阶段，5-HT 神经元放电频率下降，上行唤醒系统所受的单胺能驱动随之减弱，皮层兴奋水平下调，从而有利于睡眠启动与维持。

### 1.2.3 5-HT 对 NREM/REM 睡眠结构的调控

在 NREM 期，5-HT 神经元活动较清醒期显著降低但并非完全静默，突触间 5-HT 水平维持在较低稳态。此时

5-HT 通过 5-HT1A 受体抑制觉醒相关脑区(如蓝斑核的去甲肾上腺素能神经元), 从系统层面削弱上行唤醒驱动, 促进 NREM 的启动与巩固[10]。同时, 5-HT 还能促进视前区腹外侧等 γ-氨基丁酸(gamma-aminobutyric acid, GABA)能神经元的活性, 从而进一步通过抑制单胺能核团实现对 NREM 的间接支持[11]。

当进入 REM 期, 5-HT 与去甲肾上腺素等单胺能神经元总体放电降至极低水平, 被认为是 REM 发生的必要条件之一[12]。其生理基础在于: 5-HT 对脑桥被盖部脚桥/背外侧被盖的胆碱能 REM-on 神经元具有抑制效应, 5-HT 紧张度下降可解除该抑制, 允许胆碱能网络主导 REM 的发生与维持。受体层面, 5-HT1A 与 5-HT2A 受体的激活均表现为对 REM 的抑制效应, 从而提高 REM 阈值或缩短其持续时间。值得注意的是, 最新研究发现, 在 REM 睡眠期间, 缝核 5-HT 神经元并非完全静默, 而是出现低频或相位性簇状放电, 表明 5-HT 对 REM 的调控更可能是一种“低水平门控”过程, 而非简单的“开-关”式调节[13]。

## 2　5-HT 通路异常与睡眠障碍

围绕“代谢-受体-节律”3 条主线, 现有证据表明 5-HT 通路任一环节的功能偏移均可重塑睡眠—觉醒结构。在代谢层面, 5-HT 总体张力偏低与失眠密切相关: 代谢酶(如 MAO)活性升高会加速 5-HT 清除, 而合成限速酶 TPH(以中枢 TPH2 为主)活性下降则降低 5-HT 生成, 二者共同削弱对上行唤醒系统的抑制作用, 导致高警觉与睡眠碎片化[14]; 相反, 当 5-HT 张力系统性升高时, 过量的 5-HT 会抑制运动皮层与运动单位的兴奋性, 从而出现嗜睡或中枢性疲劳[15]。在受体层面, 不同亚型间的失衡进一步放大上述效应: 5-HT1A 信号增强与入睡潜伏期缩短、觉醒次数减少与 NREM 增加相关, 而 5-HT2A 过度激活则指向慢波睡眠(slow wave sleep, SWS、NREM 的深睡成分)减少与觉醒增多; 5-HT7 主要参与昼夜相位与 REM 门控, 其活性受抑多伴 REM 缩短与潜伏期延长[16]。药理与临床干预的“反向验证”与这一模式一致: 5-HT1A 激动剂普遍呈镇静-促睡效应, 5-HT2A 拮抗/逆向激动剂则可增加 SWS、减少入睡后觉醒并改善睡眠维持[17]。

据此, 可以将 5-HT 与睡眠的关系概括为“U 形窗口”模型, 即过低张力(合成不足、代谢过强或 1A 信号弱)倾向失眠/高警觉, 过高张力(外突触溢流或 2A 过度活化)倾向嗜睡/疲劳, 而适度张力并维持 1A/2A/7 的相对平衡与节律同步更有利于 NREM/REM 构成与睡眠连续性。该模式为以睡眠调节为目的的功能食品干预提供了 3 类明确入口, 包括底物供给与合成支持(如 Trp/5-HTP 及其辅因子以提升合成能力)、受体偏向化温和调节(增强 1A、适度拮抗 2A、协同 7 的节律校时)以及肠-脑轴重塑(通过益生菌/益生元与代谢产物影响外周 5-HT 产生与回收), 从而为开发“基于 5-HT 通路”的睡眠健康促进型功能食品提供可验证的靶点与路径。

## 3　基于 5-HT 通路改善睡眠的功能性成分研究进展

基于前述“5-HT 张力-受体-节律”框架, 本节重点综述以食源性原料及其活性成分为基础的干预研究, 包括富色氨酸原料及其代谢产物、植物提取物、益生菌/益生元及其代谢物等(表 1)。在部分研究中, 中药复方或中成药常作为整体干预形式出现, 其中既包含药用成分, 也包含酸枣仁、茯苓、百合、龙眼肉等食药同源原料。本文在引用此类研究时, 主要关注其所反映的 5-HT 相关作用通路及食源性组分的潜在贡献, 将其视作功能性食品与功能性成分开发的机制和配伍启示, 而非直接将该类制剂界定为功能食品产品形态。

### 3.1　Trp 代谢轴相关食源性功能成分及其睡眠调节作用

在合成端, 多项研究表明通过上调 TPH 活性可提升 5-HT 张力并改善睡眠表型。例如, 以酸枣仁和藤茶等食源性原料为主要成分的复合制剂能够在动物试样中逆转 *DL*-4-氯苯丙氨酸诱导的 TPH 活性下调, 从而恢复脑内 5-HT 的水平[18]; 此外, 一些传统中药复方如柴胡疏肝散[19]与逍遥散[20]也能够诱导 TPH 活性上调, 表明通过“提高合成端”对 5-HT 功能低下型失眠具有潜在益处。在肠道层面, 部分梭状芽孢杆菌[21]与产气荚膜梭菌[22]可上调结肠 TPH1 表达、促进外周 5-HT 生物合成, 并经肠-脑轴调节中枢觉醒网络, 为“经外周调中枢”提供菌群-内分泌学依据。

相反, 在 5-HT 张力过高或觉醒环路过度活化的状态下, 部分活性成分通过“降低合成/加速代谢”可产生镇静-安眠效应。例如, 博落回散的主要活性成分血根碱能够与 AADC 的巯基结合致酶失活, 理论上抑制 5-HT 的生成, 但对睡眠效果尚缺直接验证[23]。MAO 是 5-HT 降解的关键酶, 柴胡加龙骨牡蛎汤[21]与丁香酚[24]被报道可提升 MAO 活性、降低 5-HT 水平并呈现镇静-安眠倾向, 但对睡眠结构(如 NREM/REM 构成与连续性)的量化评估仍需进一步规范。

然而, Trp 并非仅流向 5-HT 通路, 有约 95%的 Trp 进入 KYN 通路, 仅 1%~2%用于合成 5-HT[25]。其中, IDO 以及 TDO2 是 KYN 通路的主要限速酶, 参与神经保护/神经毒性、免疫调节与稳态维持。在炎症或感染状态下, 细胞因子(尤其干扰素-γ)可显著诱导 IDO/TDO2 表达, 将 Trp“分流”至 KYN 通路, 导致 5-HT 合成底物相对不足, 进而降低中枢与外周 5-HT 水平。同时, KYN 下游产物喹啉酸与犬尿喹啉酸异常积累: 前者具有兴奋性神经毒性, 后者虽具神经

表 1 调控 5-HT 通路改善睡眠的食源性成分研究进展

Table 1 Research progress on food-derived components that modulate the 5-HT pathway to improve sleep

| 对象 | 调控方向 | 食源性成分/植物来源制剂 | 主要作用机制 |
|---|---|---|---|
| Trp 及其代谢产物 | TPH | 酸枣仁-藤茶酒、柴胡疏肝散、逍遥散 | 诱导 TPH 活性上调, 提高 5-HT 合成 |
| | AADC | 博落回散 | 与酶巯基结合致失活, 抑制 5-HT 生成 |
| | MAO | 柴胡加龙骨牡蛎汤、丁香酚 | 提升 MAO 活性, 加速 5-HT 清除, 降低 5-HT 水平 |
| | IDO/TDO2 (KYN 途径) | 藏红花、酸樱桃、茶叶儿茶素 | 抑制 IDO/TDO2, 减少 Trp 向 KYN 分流 |
| | 炎症因子 | 黄芪、黄花菜 | 下调炎症因子表达, 降低 IDO 活性 |
| 5-HT | 提升含量 | 酸枣仁、胡椒、夜仁合、蝉蜕、缬草、薏米, 酸枣仁-茯苓粉、桂枝加龙骨牡蛎汤、益生菌发酵发芽谷物复合物、半夏薏米汤; 芳香疗法(沉香、薰衣草等) | 上调中枢及外周 5-HT 含量, 协同调节 GABA、NE、褪黑素, 改善睡眠结构 |
| | 受体靶向 | 崖柏熏香、四逆散冻干粉、脑宁糖浆、酸枣仁、逍遥散 | 增强 5-HT1A 信号; 温和抑制 5-HT2A; 调节 5-HT7, 优化入睡潜伏期与 NREM/REM 结构 |
| 肠-脑轴 | 菌群调控 | 六堡茶、四君子汤、百合地黄汤、甘麦大枣茶、复方阿胶膏、酸枣仁制剂、益生菌、益生元、后生元 | 恢复肠道稳态, 促进 TPH1-5-HT 通路激活, 提高睡眠质量 |
| | 代谢物-SCFAs | 膳食纤维 | SCFAs 刺激肠道中 EC 细胞上调 TPH1, 促进 5-HT 生成 |
| | 代谢物-BA | - | 上调 TPH1 表达; 激活 GPBAR1/TGR5 与 FXR, 促进 5-HT 释放 |
| | TA-TAAR | - | 影响睡眠-代谢-免疫通路 |

注: 表中部分传统中药复方按现行法规属于药物范畴, 此处仅作为 5-HT 通路机制与食源性靶点的参考, 不将其视为功能食品。-表示无此项。吲哚胺-2,3-双加氧酶(indoleamine 2,3-dioxygenase 1, IDO); Trp-2,3-双加氧酶(tryptophan 2,3-dioxygenase, TDO2); 去甲肾上腺素(norepinephrine, NE); G 蛋白偶联胆汁酸受体 1 (G protein-coupled bile acid receptor 1, GPBAR1/TGR5); 法尼醇 X 受体(farnesoid X receptor, FXR); TA 相关受体(trace amine-associated receptor, TAAR)。

保护潜力, 但是过度升高会抑制谷氨酸能与胆碱能传递[26]。上述改变均可能破坏睡眠结构与稳态。基于此, 部分食源性成分被用于干预“分流”与炎症枢纽: 研究发现, 藏红花提取物[27]、酸樱桃汁[28]以及茶叶儿茶素[29]能够抑制 IDO/TDO2 活性, 减少 Trp 向 KYN 通路的分流以逆转睡眠结构紊乱; 而黄芪提取物[30]以及黄花菜乙醇提取物[31]通过下调炎症相关细胞因子的表达而降低 IDO 的表达。这些结果表明, 功能成分通过降低 Trp 向 KYN 通路的异常分流, 具有从源头调节代谢走向并恢复 5-HT 合成的潜在可行性。

### 3.2 天然活性成分调控 5-HT 通路的研究现状

多种植物来源的活性成分通过影响 5-HT 及相关神经递质实现催眠-镇静效应。以酸枣仁为代表, 其皂苷和生物碱可上调大脑皮质与海马 5-HT 含量来调控睡眠[32], 其特有的活性成分斯皮诺素可以调节 5-HT 的含量并且降低 NE 含量从而起到镇静催眠功效。其他具有明确食源属性或食药同源基础的材料, 如胡椒[33]、蝉蜕[34]等, 在动物模型中普遍呈现“上调 GABA 与 5-HT/MT), 下调谷氨酸与 NE”的神经化学谱与“减少觉醒驱动、提高慢波成分”的方向一致。

配伍层面, 酸枣仁-茯苓粉[35]、桂枝加龙骨牡蛎汤[36]、益生菌发酵发芽谷物复合物[37]与半夏薏米汤[38]等也显示出对睡眠-觉醒状态向正常化的推动, 表明“多靶点轻度调节”的组合策略在生理睡眠改善上具有潜力。在受体靶向方面, 部分天然干预可偏向性地增强 5-HT1A 信号或对 5-HT2A/5-HT7 形成功能性调节, 例如: 崖柏熏香在睡眠剥夺模型中可提升脑内 5-HT1A 受体水平, 与“缩短潜伏、减少觉醒”的表型方向一致[39]; 四逆散冻干粉、脑宁糖浆、酸枣仁与逍遥散等亦被报道经由受体与多递质通路综合作用而改善睡眠[40–42]。此外, 芳香疗法作为低风险的非药物干预, 被认为通过鼻-嗅觉化学感受与边缘系统激活影响 5-HT 及 GABA 信号, 已成为失眠管理的常见辅助手段。中国沉香、薰衣草等在动物及部分人群研究中呈现“提高 5-HT/GABA、改善睡眠表现”的一致线索, 但不同精油/香材在剂量、时相与暴露方式上的异质性提示仍需更严格的对照研究与客观睡眠指标的验证[43–45]。整体来看, 以 5-HT 为主、GABA/NE/MT 为协同轴的“多靶点轻度校正”是天然活性成分的共性机制, 其优势在于安全性与依从性, 但证据强度有赖于更多高质量临床试验的累积。

### 3.3 食源性干预通过肠-脑轴调控 5-HT 的睡眠改善机制

微生物群-肠-脑轴与睡眠之间存在双向作用: 微生物代谢物可直接影响肠-脑信号, 免疫介导的炎症-抗炎平衡可间接塑形睡眠, 而睡眠/昼夜节律本身又反过来改变微

生物群组成与功能。人体超过 90%的 5-HT 是由肠嗜铬细胞(enterochromaffin, EC)合成与释放[46], 部分孢子形成的厌氧菌群可促进肠道 5-HT 生物合成与释放, 从而影响迷走-中枢回路与节律同步[47]。在睡眠障碍相关模型与人群观察中, 失眠常伴肠道菌群结构改变(如放线菌门上升、蓝藻下降), 且与症状严重度呈相关[48], 表明“菌群-5-HT-睡眠”的三元耦联。干预证据亦在增多: 每日补充格氏乳杆菌可通过肠-脑轴显著改善轻中度睡眠问题[49]。此外, 多种食药同源类补益配方(六堡茶[50]、四君子汤[51]、百合地黄汤[52]、甘麦大枣茶[53]、复方阿胶膏[54]、酸枣仁制剂[55–56]等)被报道有助于恢复肠道微生态稳态并改善睡眠相关症状。与此同时, 益生菌、益生元与后生元通过调节菌群代谢与上调 TPH1-5-HT 通路、调和免疫炎症, 也为非药物改善睡眠提供了可复制路径[57–59]。需要强调的是, 菌群-5-HT 链条的个体差异较大, 干预效果受基础微生态与饮食结构影响明显, 因此在功能食品开发中应重视“人群分层-菌群表型-剂量与时相”的适配设计。

除菌群组成外, 代谢物信号也是肠–脑轴作用的关键中介。(1) SCFAs 作为膳食纤维发酵的主要产物, 可直接刺激肠道中 EC 细胞上调 TPH1 表达, 促进 5-HT 生成[21]; 高纤维膳食通过重塑微生物群并增加 SCFAs 形成, 被报道与外周 5-HT 表达上调、神经炎症抑制相关[60]。(2) BA 信号亦参与调控: 初级胆汁酸胆酸、鹅脱氧胆酸以及在肠道形成的次级胆汁酸脱氧胆酸可上调 TPH1 表达并促进 5-HT 升高[61]; 在高脂肪饮食模型中, 5-HT 与 TPH1 的升高常与 DCA、CA 水平上升并行[62]; 相应地, BA 受体 GPBAR1/TGR5 与 FXR 的激活被证实可促进 5-HT 释放[63]。(3)微生物来源的 TA(如 $\beta$-苯乙胺、对-酪胺、色胺)可作用于 TAAR 并与睡眠、代谢和免疫调节相关[64]。TAAR1 信号与胃肠系统的密切联系表明“肠源性 TA-TAAR-脑”的潜在通路, 为靶向脑-肠-微生物组轴的干预提供了新方向[65–66]。

## 4　食源性功能成分与其他干预措施的协同应用

### 4.1　食源性功能成分与物理刺激技术的联合应用

物理刺激技术通过直接或间接影响皮层兴奋性与昼夜时钟, 为功能食品的 5-HT 调控提供了协同“窗口”。重复经颅磁刺激(repeated transcranial magnetic stimulation, rTMS)与经颅电刺激(transcranial direct current stimulation, tDCS/tACS)在无创条件下调节特定皮层区的神经活动与网络连通性, 从而间接作用于缝核-前额叶-边缘系统等与 5-HT 通路交互的环路[67]; 光照疗法(包括阻断蓝光与定时明亮光)通过 SCN-MT 轴重置昼夜相位, 与“5-HT→MT”代谢链路存在上、下游耦联[68]; 低频摇动/振动能增强 NREM2 与睡眠纺锤活动, 降低觉醒倾向。在传统技术方面, 针灸、艾灸、拔罐与耳穴压豆等被反复用于失眠管理, 既往报道多采用与中药/功能食品的联合: 如针刺分别与安神类方剂或补益类方(丹栀逍遥散[69]、柴胡加龙骨牡蛎汤[70–71]、壮药五味子合剂[72]、温肾养肝中药[73]、清肝安神汤[74]、半夏泻心汤[75]等)配伍用于不同证型的失眠, 显示较单一干预更优的睡眠改善趋势; 艾灸与安眠茶[76]、枣仁安寐汤[77]、瓜蒌麦芽汤[78]、温和灸联合归脾汤[79]联合, 拔罐与黄连温胆汤、和胃安神汤等联合[80–83], 耳穴压豆与养心/疏肝安神类方(毛氏安神方[84]、养心安神汤[85]、自拟养心健脾汤[86]柴胡加龙骨牡蛎汤[87])联合, 亦报道可提升总睡时、睡眠效率与主观睡眠质量。芳香疗法(薰衣草、苏合香、沉香、蛇麻草、佩兰等)通过嗅觉-边缘系统-自主神经的通路影响 GABA/5-HT 张力, 可作为非药物的时相化辅助, 与功能食品在睡前“同相”使用以巩固入睡窗口[88–92]。运动与身心技术(八段锦[93]、瑜伽[94]、慢跑[95]、高强度间歇训练[96]、太极[97])通过下调高警觉与炎症水平、同步外周时钟而改善睡眠结构, 与功能食品(如富 Trp 蛋白/多肽、益生菌等)的长期联用更有利于保持昼夜-代谢-情绪的一致性。在新技术与复合方案方面, rTMS 或 tDCS 与安神/补益类中药汤剂联用的探索增多(如滋肾心安神汤、归脾汤、人参养荣汤)[98–100]; 益生菌与 tDCS 的组合也显示对特殊人群(如脑卒中后认知障碍)睡眠质量的改善潜力, 表明“微生态→5-HT→皮层可塑性”的跨通路协同[101]。

总体而言, 基于天然来源成分的干预与物理刺激技术联合的策略在理论上主要体现在两方面优势: 其一, 时相协同——在睡前/夜间以功能食品平稳回调或维持 5-HT 张力, 同时按时程实施物理刺激以降低皮层高警觉或校正昼夜相位, 从而在同一生理窗口内形成合力; 其二, 多靶点微调——以低强度、方向一致的方式同步作用于 5-HT 的合成/降解、受体偏向与节律环路及皮层网络, 更易在保证安全性的前提下获得结构性睡眠收益。现阶段证据仍以小样本、非随机或非盲研究为主, 外推性有限。后续研究宜采用严格的随机对照设计, 纳入客观睡眠指标与昼夜相位生物标志, 并按表型分层(入睡困难型、维持障碍型、节律错位型等)以明确不同人群的最佳时相与剂量方案。

### 4.2　食源性功能成分及中药制剂与药物的联合干预

在以药物治疗为主的临床场景中, 食源性功能成分或含食药同源原料的制剂可在一定条件下作为辅助干预, 通过降低药物必要剂量、缓冲不良反应及改善日间功能等途径发挥增效作用。围绕 5-HT 通路的联合研究大体可分为 3 类: (1)与抗抑郁或促 5-HT 药物的协同: 含酸枣仁等食药同源原料的复方制剂(如舒眠胶囊)联合曲唑酮可共同影响 5-HT 合成、释放与再摄取, 改善睡眠质量[102]; 部分中药制剂(如天麻钩藤饮、疏肝安神汤)与帕罗西汀联用, 同向作用于 1A/2A 受体偏向化与高警觉下调[103–104]; (2)与镇静催眠或抗焦虑药物的配伍: 如养血安神膏与艾司唑仑、维

生素 D 与右佐匹克隆、枣仁安神胶囊与劳拉西泮等组合，在缩短入睡潜伏、延长总睡时、减少夜间觉醒方面显示优势[105–107]；(3)与神经调控药物或特定人群用药的联合：益生菌与多巴胺类药物在帕金森病或共病人群中的联合可同时改善睡眠与胃肠症状[108]；乌灵胶囊与思诺思(右佐匹克隆/唑吡坦类)或与普拉克索联用，分别在焦虑伴失眠与帕金森病伴失眠中显示协同[109–110]；此外，养血清脑颗粒与硝苯地平或右佐匹克隆、养心汤与氟哌噻吨-美利曲辛、疏肝解郁胶囊与阿立哌唑等组合也有积极信号[111–114]。

这些“以中药制剂或天然来源成分为辅助的药物联合方案”在机制上具有一定共性：通过温和拉回 5-HT 张力到第 2 部分所述的“适度区间”，并在受体层面形成偏向化调节(增强 1A、适度抑制 2A/7)，从而改善睡眠结构与主观睡眠质量。然而，安全性边界必须明确：与选择性血清素再摄取抑制剂和血清素/去甲肾上腺素再摄取抑制剂曲唑酮、单胺氧化酶抑制药等促 5-HT 药物联用时，应警惕潜在的 5-HT 相关不良反应；与镇静催眠药联用时需关注叠加镇静、认知、跌倒风险；草本复方还可能通过细胞色素 P450 超家族代谢酶或转运体产生药动学相互作用。因此，推荐在医生指导下进行个体化用药/用食调整，并在研究中报告剂量、给药时相、依从性及不良事件。

## 5 结束语

本文在 5-HT“张力-受体-节律”框架下梳理了 5-HT 通路与睡眠的关系，并以“U 形窗口”模型概括其规律，即张力过低偏向失眠/高警觉，过高偏向嗜睡/中枢性疲劳，适度张力配合 5-HT1A/5-HT2A/5-HT7 信号平衡与昼夜相位同步，有利于优化 NREM/REM 构成与睡眠连续性。围绕该模型，当前研究表明与 5-HT 通路相关的食源性功能成分主要通过 3 条路径发挥潜在助眠作用：(1)底物补充与合成支持，通过 Trp、5-HTP 及其辅因子温和提升合成效率；(2)受体偏向化的多靶点轻度调节，增强 1A 受体活性、适度抑制 2A 受体并协同 7 受体的节律校时；(3)肠-脑轴重塑，利用益生菌、益生元或其代谢物上调外周 TPH1-5-HT 通路并改善微生态稳态。同时，食源性干预若与光照、rTMS/tDCS、运动或低剂量药物等干预在时间上实现“相位化协同”，有望产生更显著的综合促进效应。

当前研究仍受限于样本量小、设计异质性高、原料及成分定量标准化不足、联合干预安全性与个体差异等问题。未来应开展纳入节律指标与“进食时相(时间营养学)”设计的多中心临床试验；建立覆盖“成分-指纹图谱-生物标志物”的质量控制体系，关注关键成分的体内转化与生物利用度；结合多组学与网络药理学技术，解析“菌群-代谢物-TPH1/5-HT-迷走-中枢”的跨层效应链；并在基因与微生态分层基础上推进个体化验证与真实世界随访，逐步形成可评价、可复制、可推广的基于 5-HT 通路的睡眠健康功能食品研发与应用方案，从而实现从机制研究到产品开发的有效衔接。

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