

doi: 10.13241/j.cnki.pmb.2021.08.007

## 黄芩苷对慢性萎缩性胃炎模型鼠 OPG/RANKL 轴的影响 \*

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**摘要 目的:**探讨黄芩苷对慢性萎缩性胃炎模型鼠 OPG/RANKL 轴的影响。**方法:**将建模成功的大鼠(n=42)平分为三组-模型组、雷尼替丁组与黄芩苷组,黄芩苷组灌胃 6.3 g/kg 体重的黄芩苷溶液(5 mg·kg<sup>-1</sup>),雷尼替丁组灌胃 6.3 g/kg 体重的雷尼替丁生理盐水溶液(150 mg·kg<sup>-1</sup>),模型组灌胃与同容积的生理盐水,记录不同时间点 OPG/RANKL 轴表达变化情况。**结果:**雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的体重高于模型组(P<0.05),黄芩苷组高于雷尼替丁组(P<0.05)。雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的胃黏膜组织评分低于模型组(P<0.05),黄芩苷组低于雷尼替丁组(P<0.05)。雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的血清 NO 与 SOD 含量高于模型组 (P<0.05),黄芩苷组高于雷尼替丁组 (P<0.05)。雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的胃窦组织 OPG、RANKL 蛋白相对表达水平高于对照组,黄芩苷组高于雷尼替丁组(P<0.05)。**结论:**黄芩苷治疗慢性萎缩性胃炎模型鼠能激活 OPG/RANKL 轴,提高血清 NO 与 SOD 含量,能减少胃黏膜组织损伤,提高大鼠体重。

**关键词:**黄芩苷;慢性萎缩性胃炎;大鼠;OPG/RANKL 轴;氧化应激

中图分类号:R-33;R573.32 文献标识码:A 文章编号:1673-6273(2021)08-1434-04

## Effects of Baicalin on OPG/RANKL Axis of Chronic Atrophic Gastritis Model Rats\*

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**ABSTRACT Objective:** To investigate the effects of baicalin on OPG/RANKL axis of chronic atrophic gastritis model mice. **Methods:** The successfully modeled rats (n=42) were equally divided into three groups-model group, ranitidine group and baicalin group. Baicalin group was given intragastrically 6.3 g/kg baicalin solution (5 mg·kg<sup>-1</sup>); the ranitidine group was given intragastrically with 6.3 g/kg body weight ranitidine saline solution (150 mg·kg<sup>-1</sup>); the model group was given intragastrically with the same volume of saline solution. OPG/RANKL axis expression changes were recorded at different time points. **Results:** The body weight of the ranitidine group and the baicalin group were higher than that of the model group 2 and 4 weeks after treatment (P<0.05), and the baicalin group was higher than the ranitidine group (P<0.05). The gastric mucosal tissue scores of the ranitidine group and the baicalin group were lower than the model group 2 and 4 weeks after treatment (P<0.05), and the baicalin group was lower than the ranitidine group (P<0.05). The serum NO and SOD levels of the ranitidine group and the baicalin group were higher than those of the model group 2 and 4 weeks after treatment (P<0.05), and the baicalin group was higher than the ranitidine group (P<0.05). The relative expression levels of OPG and RANKL protein in gastric antrum tissue in the ranitidine group and the baicalin group were higher than those in the model group 2 and 4 weeks after treatment (P<0.05), and the baicalin group was higher than the ranitidine group (P<0.05). **Conclusion:** In the treatment of chronic atrophic gastritis model mice, baicalin can activate OPG/RANKL axis, increase serum NO and SOD content, reduce gastric mucosal tissue damage, and increase rat body weight.

**Key words:** Baicalin; Chronic atrophic gastritis; Rats; OPG/RANKL axis; Oxidative stress

**Chinese Library Classification (CLC):** R-33; R573.32 **Document code:** A

**Article ID:** 1673-6273(2021)08-1434-04

### 前言

慢性萎缩性胃炎(chronic atrophic gastritis, CAG)为慢性胃炎的主要类型之一,为胃黏膜上皮遭受反复损害导致固有层腺

体的减少的慢性胃部疾病<sup>[1]</sup>。该病在临床上的病理特征为胃黏膜上皮和腺体萎缩、黏膜基层增厚、黏膜变薄、伴幽门腺化生和肠腺化生,具有病因病机复杂多变等特征,可严重影响患者的身心健康<sup>[2,3]</sup>。现代医学对慢性萎缩性胃炎尚缺乏理想的治疗措

\* 基金项目:陕西省重点研发计划项目(2019-SF-219)

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(收稿日期:2020-10-09 接受日期:2020-10-31)

施,以对症治疗、缓解症状为主,使用保护胃黏膜、增强胃动力、抗幽门螺杆菌等药物,具有治疗周期长、疗效有效、花费高、不良反应多等不足<sup>[4]</sup>。该病在中医学上可被归为"痞证"、"积滞"、"腹胀"、"胃脘痛"、"嘈杂"等范畴,药物所伤、劳倦过度、外邪侵袭、饮食不节、情志失调可影响脾胃运化功能,久致使气血生化失常,胃络失养<sup>[67]</sup>。黄芪是健脾益气类中药的代表药物,具有托毒生肌、补气固表之功效<sup>[8]</sup>。而黄芩苷是黄芪主要成分之一,为一种单体皂苷类化合物,可促进胃粘膜细胞增殖,抑制胃粘膜细胞凋亡,从而发挥保护胃粘膜的作用<sup>[9,10]</sup>。OPG/RANKL轴是影响机体内环境的重要信号通路,OPG为一种可溶性糖蛋白,是胃功能重建的关键因子<sup>[11]</sup>;RANKL可以促进破骨细胞前体细胞分化为破骨细胞,并增强其活性,也有一定的胃保护功能<sup>[12]</sup>。本文具体探讨了黄芩苷对慢性萎缩性胃炎模型鼠OPG/RANKL轴的影响,希望为治疗慢性萎缩性胃炎提供理论及实验依据。

## 1 材料与方 法

### 1.1 主要研究材料

实验用清洁级雄性 Wistar 大鼠 60 只(n=48,体重 200~240 g)购于南京君科生物工程有限公司(动物合格证编号:SYXK20200021),实验期间保证大鼠自由饮水和进食,室内温度设定为 20℃~24℃,相对湿度 45%~65%。饮用水采用清洁级自来水,饲料购自南京君科生物工程有限公司。实验过程中所有动物处置方式符合动物伦理学标准。黄芩苷生理盐水溶液由成都思科华生物技术有限公司,NO、SOD 检测试剂盒购自大连 TAKARA 公司,抗 OPG 抗体、抗 RANKL 抗体购自美国 sigma 公司,雷尼替丁购自赛诺菲安万特制药有限公司,N-甲基-N'-硝基-N'-亚硝基胍(MNNG)购自日本东京化成工业发展有限公司。

### 1.2 动物建模与分组

所有大鼠都给予建立慢性萎缩性胃炎模型,每日自由饮用

2%水杨酸钠溶液,每日灌胃 120 μg/mL MNNG),每周禁食 1 次,每次 18 h,持续应用 4 w。将建模成功的大鼠(n=42)平分为三组-模型组、雷尼替丁组与黄芩苷组,每组根据在治疗后 2 w 与 4 w 各分为两个亚组,每组 7 只。雷尼替丁组:灌胃 6.3 g/kg 体重的雷尼替丁生理盐水溶液(150 mg·kg<sup>-1</sup>),1 次/d,共 4w;黄芩苷组:灌胃 6.3 g/kg 体重的黄芩苷溶液(5 mg·kg<sup>-1</sup>),1 次/d,共 4 w;模型组:灌胃与同容积的生理盐水,1 次/d,共 4 w。

### 1.3 观察指标

(1)在治疗第 2 w、第 4 w 测定与记录大鼠的体重。(2)处死大鼠后,取胃黏膜组织,制成病理切片后进行评分,轻度(2 分):固有腺体数减少数量 < 原有腺体的 1/3;中度(4 分):固有腺体数减少数量在原有腺体的 1/3-2/3 之间;重度(6 分):固有腺体数减少数量 > 原有腺体的 1/3,仅残留少数腺体甚或完全消失。(3)取处死动物的心脏血,血液离心取上清,采用全自动生化分析仪测定血清 NO、SOD 含量。(4)取处死动物的胃窦黏膜组织,提取总蛋白,采用 Western blot 检测 OPG、RANKL 蛋白表达水平。

### 1.4 统计方法

全部实验数据均采用 SPSS 18.00 统计软件包处理,计量数据采用均数±标准差表示,两两对比为 t 检验,多组间对比为单因素方差分析,以 P<0.05 为有统计学差异。

## 2 结果

### 2.1 大鼠一般情况对比

模型组:大鼠毛色干枯无光泽,体重减轻,大便不成形,动物的活动及饮食相应减少。

雷尼替丁组与黄芩苷组:大鼠毛色渐润泽,摄食、体重等相应增加,活动也趋于正常。

### 2.2 大鼠体重对比

雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的体重高于模型组(P<0.05),黄芩苷组高于雷尼替丁组(P<0.05),见表 1。

表 1 三组治疗后不同时间点的体重对比(g,  $\bar{x} \pm s$ )

Table 1 Comparison of body weight at different time points after treatment among three groups (g,  $\bar{x} \pm s$ )

Groups	n	2 weeks after treatment	4 weeks after treatment
Model group	7	266.34± 12.48	287.09± 14.28
Ranitidine group	7	278.98± 21.00*	309.87± 13.11*
Baicalingroup	7	289.11± 13.748*#	317.87± 15.66*#
F		12.933	18.723
P		0.000	0.000

Note: compared with the model group, \*P<0.05; compared with the ranitidine group, #P<0.05.

### 2.3 大鼠胃黏膜组织评分对比

雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的胃黏膜组织评分低于模型组(P<0.05),黄芩苷组低于雷尼替丁组(P<0.05),见表 2。

### 2.4 血清 NO 与 SOD 含量对比

雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的血清 NO 与 SOD 含量高于模型组(P<0.05),黄芩苷组高于雷尼替丁组(P<0.05),见表 3。

### 2.5 OPG、RANKL 蛋白相对表达水平对比

雷尼替丁组与黄芩苷组治疗后 2 w 与 4 w 的胃窦组织 OPG、RANKL 蛋白相对表达水平高于对照组,黄芩苷组高于雷尼替丁组(P<0.05),见表 4。

## 3 讨论

慢性萎缩性胃炎是消化系统难治病,在临床上主要表现为胃脘不适、食纳不振、胀满、隐痛、暖气、形体消瘦、面色萎黄等<sup>[13,14]</sup>。当前治疗该病无特效药,中医药整体治疗疗效甚佳,不但能缓解症状,在延缓疾病方面也有一定优势。黄芪为临床上

表 2 三组治疗后大鼠胃黏膜组织评分(g,  $\bar{x} \pm s$ )

Table 2 Comparison of gastric mucosal tissue scores after treatment among three groups (g,  $\bar{x} \pm s$ )

Groups	n	2 weeks after treatment	4 weeks after treatment
Model group	7	5.36± 0.11	5.20± 0.11
Ranitidine group	7	2.83± 0.09*	2.58± 0.14*
Baicalingroup	7	1.67± 0.14**	1.54± 0.18**
F		19.723	20.742
P		0.000	0.000

Note: compared with the model group, \*P<0.05; compared with the ranitidine group, #P<0.05.

表 3 三组治疗后不同时间点的血清 NO 与 SOD 含量对比( $\bar{x} \pm s$ )

Table 3 Comparison of serum NO and SOD levels among three groups at different time points after treatment ( $\bar{x} \pm s$ )

Groups	n	NO( $\mu\text{mol/L}$ )		SOD(U/mL)	
		2 weeks after treatment	4 weeks after treatment	2 weeks after treatment	4 weeks after treatment
Model group	7	8.14± 0.24	8.78± 0.32	132.76± 12.47	137.87± 13.00
Ranitidine group	7	14.09± 1.44*	15.02± 1.11*	187.65± 13.02*	189.00± 12.47*
Baicalingroup	7	17.87± 1.41**	18.09± 1.24**	197.88± 12.64**	200.76± 14.11**
F		9.813	9.113	17.382	17.725
P		0.000	0.001	0.000	0.000

Note: compared with the model group, \*P<0.05; compared with the ranitidine group, #P<0.05.

表 4 三组治疗后不同时间点的胃窦组织 OPG、RANKL 蛋白相对表达水平对比( $\bar{x} \pm s$ )

Table 4 Comparison of relative expression levels of OPG and RANKL proteins in gastric antrum tissues among three groups at different time points after treatment ( $\bar{x} \pm s$ )

Groups	n	OPG		RANKL	
		2 weeks after treatment	4 weeks after treatment	2 weeks after treatment	4 weeks after treatment
Model group	7	1.03± 0.12	1.19± 0.14	0.98± 0.18	1.00± 0.10
Ranitidine group	7	2.18± 0.02*	2.31± 0.11*	1.87± 0.16*	1.99± 0.25*
Baicalingroup	7	3.27± 0.18**	3.33± 0.17**	3.18± 0.19**	3.33± 0.17**
F		9.133	8.724	9.013	9.284
P		0.001	0.002	0.001	0.001

Note: compared with the model group, \*P<0.05; compared with the ranitidine group, #P<0.05.

常见的传补气良药, 黄芪苷是黄芪药理活性主要物质之一, 也是一种单体皂苷类化合物, 也被作为黄芪质量检测标志物<sup>[15]</sup>。黄芪苷可通过抑制胃粘膜细胞凋亡, 对胃粘膜损害具有较好保护作用, 可促进胃粘膜细胞增殖<sup>[16]</sup>。本研究显示雷尼替丁组与黄芪苷组治疗后 2 w 与 4 w 的体重高于模型组, 黄芪苷组高于雷尼替丁组; 雷尼替丁组与黄芪苷组治疗后 2 w 与 4 w 的胃黏膜组织评分低于模型组, 黄芪苷组低于雷尼替丁组, 表明黄芪苷治疗慢性萎缩性胃炎模型鼠能减少胃黏膜组织损伤, 提高大鼠体重。当前也有研究显示黄芪苷对大鼠胃粘膜损害具有较好保护作用, 应用黄芪苷组大鼠的胃粘膜仅有局部损伤, 能减少胃粘膜损伤面积, 模型组大鼠的胃粘膜损伤程度较重<sup>[17,18]</sup>。

慢性萎缩性胃炎在中医学上以 "痞" 及 "胀" 居多, 病机在于 "结而不散", 病变核心在于脾。该病的发生机制还不明确, 不过与氧化应激存在一定的相关性<sup>[19]</sup>。SOD 可清除超氧阴离子自由基, 是对机体氧化和抗氧化系统平衡发挥重要作用的抗氧化酶, 也保护细胞免受损害<sup>[20,21]</sup>。NO 由血管内皮细胞产生, 是胃肠粘膜防御的重要因素之一, 具有调节免疫应答、扩张血管等多种功能。NO 分泌增加可减少胃酸分泌, 减少氧自由

基的产生, 提高胃粘膜的屏障保护作用, 从而减轻机体的炎症反应<sup>[22,23]</sup>。本研究显示雷尼替丁组与黄芪苷组治疗后 2 w 与 4 w 的血清 NO 与 SOD 含量高于模型组, 黄芪苷组高于雷尼替丁组, 表明黄芪苷治疗慢性萎缩性胃炎模型鼠能提高血清 NO 与 SOD 含量, 也可能是黄芪苷对胃粘膜发挥保护作用的有效途径之一<sup>[24,25]</sup>。

OPG 是由间充质细胞衍生的细胞分泌的一种糖蛋白, 广泛存在于甲状腺、肠、骨组织、心脏、胃等组织中, 其可抑制破骨细胞的增殖分化, 抑制骨吸收<sup>[25-27]</sup>。OPG 可与 RANKL 竞争性结合, 阻断信号传导, 抑制破骨细胞的活性, 减少破骨细胞的增殖分化与成熟, 调节骨重建平衡<sup>[28,29]</sup>。RANKL 能与 RANK 结合后, 激活胞质内的信号传导, 延长破骨细胞的存活时间, 抑制破骨细胞的凋亡, 延长破骨细胞的存活时间<sup>[30,31]</sup>。本研究显示雷尼替丁组与黄芪苷组治疗后 2 w 与 4 w 的胃窦组织 OPG、RANKL 蛋白相对表达水平高于对照组, 黄芪苷组高于雷尼替丁组, 表明黄芪苷治疗慢性萎缩性胃炎模型鼠能激活 OPG/RANKL 轴, 从而使萎缩性胃炎黏膜细胞的凋亡受到促进作用, 发挥胃保护作用。本研究也存在一定的不足, 大鼠样本量较小, 没有进行多

个时间点的动态分析,也没有进行治疗前分析,将在后续研究中进行探讨。

总之,黄芩苷治疗慢性萎缩性胃炎模型鼠能激活 OPG/RANKL 轴,提高血清 NO 与 SOD 含量,能减少胃黏膜组织损伤,提高大鼠体重。

#### 参考文献(References)

- [1] Avila-Carrasco L, Majano P, Sánchez-Toméro JA, et al. Natural Plants Compounds as Modulators of Epithelial-to-Mesenchymal Transition [J]. *Front Pharmacol*, 2019, 10(5): E715
- [2] He P, Wu Y, Shun J, et al. Baicalin Ameliorates Liver Injury Induced by Chronic plus Binge Ethanol Feeding by Modulating Oxidative Stress and Inflammation via CYP2E1 and NRF2 in Mice [J]. *Oxid Med Cell Longev*, 2017, 20(17): 4820-4824
- [3] Ishfaq M, Chen C, Bao J, et al. Baicalin ameliorates oxidative stress and apoptosis by restoring mitochondrial dynamics in the spleen of chickens via the opposite modulation of NF- $\kappa$ B and Nrf2/HO-1 signaling pathway during *Mycoplasma gallisepticum* infection [J]. *Poult Sci*, 2019, 98(12): 6296-6310
- [4] Li J, Qiao Z, Hu W, et al. Baicalin mitigated *Mycoplasma gallisepticum*-induced structural damage and attenuated oxidative stress and apoptosis in chicken thymus through the Nrf2/HO-1 defence pathway [J]. *Vet Res*, 2019, 50(1): E83
- [5] Perruchot MH, Gondret F, Robert F, et al. Effect of the flavonoid baicalin on the proliferative capacity of bovine mammary cells and their ability to regulate oxidative stress[J]. *PeerJ*, 2019, 7(13): e6565
- [6] Qian Y, Chen Y, Wang L, et al. Effects of baicalin on inflammatory reaction, oxidative stress and PKD1 and NF- $\kappa$ B protein expressions in rats with severe acute pancreatitis I [J]. *Braz J Med Biol Res*, 2018, 33(7): 556-564
- [7] Zhong J. Baicalin ameliorates chronic mild stress-induced depression-like behaviors in mice and attenuates inflammatory cytokines and oxidative stress[J]. *Vet Res*, 2019, 52(7): e8434
- [8] De Oliveira AF, Da Luz BB, Werner MFP, et al. Gastroprotective activity of a pectic polysaccharide fraction obtained from infusion of *Sedum dendroideum* leaves[J]. *Phytomedicine*, 2018, 41(13): 7-12
- [9] 王首帆,徐宜厚,徐爱琴,等.复方黄芩"水膜"外用治疗急性湿疹抗炎和抑制金葡菌的实验研究[J].*世界中医药*, 2019, 14(1): 81-84
- [10] 杨骥,杨雪,杨洁,等.黄芩苷对狼疮鼠肾炎的治疗作用和对滤泡辅助 T 细胞的调控作用[J].*中华皮肤科杂志*, 2019, 52(3): 167-171
- [11] Kale OE, Awodele O, Akindede AJ. Subacute and subchronic oral toxicity assessments of *Acridocarpus smeathmannii* (DC.) Guill. & Perr. root in Wistar rats [J]. *Evid Based Complement Alternat Med*, 2019, 6(12): 161-175
- [12] Kengkoom K, Tirawanchai NN, Angkhasirisap W, et al. Omeprazole preserves the RER in chief cells and enhances re-epithelialization of parietal cells with SOD and AQP-4 up-regulation in ethanol-induced gastritis rats[J]. *Exp Ther Med*, 2017, 14(6): 5871-5880
- [13] Kim YS, Jeong M, Han YM, et al. Combined Extracts of Artemisia and Green Tea, Mitigated Alcoholic Gastritis Via Enhanced Heat-shock Protein 27 [J]. *Evid Based Complement Alternat Med*, 2018, 71(3): 132-142
- [14] Kwon DA, Kim YS, Baek SH, et al. Protective effects of a standardized extract (HemoHIM) using indomethacin- and ethanol/HCl-induced gastric mucosal injury models [J]. *Pharm Biol*, 2019, 57(1): 543-549
- [15] Liu CC, Chen JL, Chang XR, et al. Comparative metabolomics study on therapeutic mechanism of electro-acupuncture and moxibustion on rats with chronic atrophic gastritis (CAG)[J]. *Sci Rep*, 2017, 7(1): e14362
- [16] Azab SS, Abdel Jaleel GA, Eldahshan OA. Anti-inflammatory and gastroprotective potential of leaf essential oil of *Cinnamomum glanduliferum* in ethanol-induced rat experimental gastritis[J]. *Evid Based Complement Alternat Med*, 2017, 55(1): 1654-1661
- [17] Bai Y, Chen Y, Chen Y, et al. Efficacy of Banxia Xiexin decoction in a rat model of chronic atrophic gastritis [J]. *J Tradit Chin Med*, 2019, 39(6): 867-874
- [18] 林少琴,张绍琴,陈思玉,等.中药组方黄芩汤抑制胃癌细胞增殖的实验研究[J].*中华细胞与干细胞杂志(电子版)*, 2019, 9(6): 340-344
- [19] Luo C, Sun Z, Li Z, et al. Notoginsenoside R1 (NGR1) Attenuates Chronic Atrophic Gastritis in Rats [J]. *Med Sci Monit*, 2019, 25(13): 1177-1186
- [20] Oswari L, Hidayat R, Fatmawati F, et al. Gambir Extract (*Uncaria Gambir*) Decreases Inflammatory Response and Increases Gastric Mucosal Integrity in Wistar Rats - Model Gastritis [J]. *Open Access Maced J Med Sci*, 2019, 7(19): 3149-3152
- [21] Park JU, Kang JH, Rahman MaA. Gastroprotective Effects of Plants Extracts on Gastric Mucosal Injury in Experimental Sprague-Dawley Rats [J]. *Evid Based Complement Alternat Med*, 2019, 20(13): 8759-8761
- [22] Saremi K, Rad SK, Tayeby F, et al. Gastroprotective activity of a novel Schiff base derived dibromo substituted compound against ethanol-induced acute gastric lesions in rats [J]. *Evid Based Complement Alternat Med*, 2019, 20(1): e13
- [23] Sohn YA, Hwang IY, Lee SY, et al. Protective Effects of Genipin on Gastrointestinal Disorders[J]. *Biol Pharm Bull*, 2017, 40(2): 151-154
- [24] 哈力达·巴合提汗,姚亚妮,韩雪洁,等.黄芩苷对帕金森病模型鼠大脑皮质及纹状体区缝隙连接蛋白 36 表达的影响 [J]. *中华医学杂志*, 2019, 99(3): 218-222
- [25] 杨宁,路强,袁梦克,等.黄芩素对缺氧诱导的视网膜神经胶质细胞中脯氨酸羟化酶 2 表达的抑制作用[J].*中华实验眼科杂志*, 2017, 35(11): 990-996
- [26] De Araújo ERD, Guerra GCB, Araújo DFS, et al. Gastroprotective and Antioxidant Activity of *Kalanchoe brasiliensis* and *Kalanchoe pinnata* Leaf Juices against Indomethacin and Ethanol-Induced Gastric Lesions in Rats[J]. *Biomed Res Int*, 2018, 19(5): 115-119
- [27] De Carvalho TG, Ferreira LS, Zucolotto SM, et al. The therapeutic effect of zerumbone on chronic gastritis via antioxidant mechanisms[J]. *Int J Mol Sci*, 2017, 14(3): 2505-2510
- [28] Szabó IL, Szabó S, Helyes Z, et al. Impaired Interoception in a Pre-clinical Model of Functional Dyspepsia[J]. *Int J Mol Sci*, 2017, 62(9): 2327-2337
- [29] Tastekin E, Ayvaz S, Usta U, et al. Indomethacin-induced gastric damage in rats and the protective effect of donkey milk [J]. *Dig Dis Sci*, 2018, 14(3): 671-678
- [30] Yu C, Su Z, Li Y, et al. Dysbiosis of gut microbiota is associated with gastric carcinogenesis in rats [J]. *Biomed Pharmacother*, 2020, 126(12): e110036
- [31] Zhang J, Wang H. Morroniside protects against chronic atrophic gastritis in rat via inhibiting inflammation and apoptosis[J]. *Am J Transl Res*, 2019, 11(9): 6016-6023