# ω-3 PUFAs 防治奥沙利铂联合卡培他滨治疗所致周围神经毒性的临床研究

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摘　要:[目的]观察 ω-3 多不饱和脂肪酸(ω-3 PUFAs)防治结肠癌患者奥沙利铂联合卡培他滨(XELOX)方案化疗所致的周围神经毒性的有效性,为防治化疗所致周围神经毒性提供临床依据。[方法] 采用随机、双盲、安慰剂对照研究,将符合纳入标准 73 例接受 XELOX 方案化疗的结肠癌患者随机分为治疗组(ω-3 PUFAs+化疗)37 例和对照组(安慰剂+化疗)36 例。各组均以 21d 为 1 个疗程,共治疗 6 个疗程。观察并分析两组患者化疗前后因奥沙利铂所致神经毒性的发生、严重程度及神经传导。[结果] 治疗组与对照组周围神经毒性发生率分别为 35.13%和 72.22%($\chi^2$=43.975,$P$<0.001), 两组周围神经病变严重程度也存在显著性差异 ($\chi^2$=47.768,$P$<0.001)。在动作及感觉神经传导方面,化疗后治疗组与对照组的腓肠神经的感觉动作电位(a-SAP)分别为(13.91±1.95)μV 和(11.08±2.01)μV($P$<0.001)。[结论] ω-3 PUFAs 能降低 XELOX 方案化疗所致的周围神经毒性发生率及严重程度, 有望成为治疗奥沙利铂所致神经毒性的潜在药物。

主题词:ω-3 多不饱和脂肪酸;奥沙利铂;周围神经病变
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## Prevention of Peripheral Neurotoxicity Caused by Oxaliplatin and Capecitabine with ω-3 PUFAs in Colon Cancer Patients

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**Abstract**:[Objective] To investigate the application of ω-3 polyunsaturated fatty acid (ω-3 PUFAs ) in the prevention and treatment of peripheral neurotoxicity caused by chemotherapy with XELOX(oxaliplatin combined with capecitabine) in patients with colon cancer. [Methods] In this randomized,double-blind,placebo-controlled clinical trial,73 patients with colon cancer who received XELOX chemotherapy were assigned into two groups,the study group (n=37) was treated with ω-3 PUFAs and chemotherapy and the control group(n=36) was treated with placebo and chemotherapy. Each course of treatment was 21 days,and all patients were treated for 6 courses. The incidence and severity of peripheral neurotoxicity caused by XELOX chemotherapy were compared between two groups,and the conduction of motor and sensory nerves was also observed in two groups. [Results] The incidence of peripheral neurotoxicity in the study group and control group were 35.13% and 72.22%($\chi^2$=43.975,$P$<0.001). There was also a significant difference in the severity of peripheral neuropathy between two groups ($\chi^2$=47.768,$P$<0.001) . The sensory action potentials (a-SAP) of the sural nerves in the study group and the control group after chemotherapy were(13.91±1.95) μV and (11.08±2.01)μV respectively($P$<0.001). [Conclusion] ω-3 PUFAs can reduce the incidence and severity of peripheral neurotoxicity caused by XELOX chemotherapy significantly,and it is expected to be a potential drug for the treatment of neurotoxicity caused by oxaliplatin.

**Subject words**:ω-3 polyunsaturated fatty acid;oxaliplatin;peripheral neuropathy

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据最新 GLOBOCAN 2018 报告,2018 年结直肠癌发生率和死亡率分别占恶性肿瘤的 6.1%和 9.2%[1]。目前,化疗仍然是结肠癌治疗的主要手段。临床研究证实,XELOX 方案不仅是结肠癌术后辅助化疗的标准方案,也是晚期结肠癌治疗中一线治疗方案[2]。奥沙利铂作为 XELOX 方案的主要药物,虽然能提高患者的总生存时间[3-4],但奥沙利铂导致的周围神经毒性仍然是化疗剂量使用的限制因素[5]。使用奥沙利铂的大部分患者会出现不同程度的周围神经毒性,但奥沙利铂神经毒性的确切发生机制还不是很清楚,主要认为与奥沙利铂本身的毒性积蓄及代谢产物草酸盐相关[6]。临床上常使用钙剂、镁剂、还原型谷胱甘肽等药物治疗,但疗效不理想,最有效的方式是暂停使用奥沙利铂。

ω-3 多不饱和脂肪酸(ω-3 polyunsaturated fatty acid,ω-3 PUFAs)是人体的必需脂肪酸,主要包含二十碳五烯酸(eicosatetraenoic acid,EPA)和二十二碳六烯酸(docosahexenoic acid,DHA)。研究发现,EPA 和 DHA 能够治疗神经退行性疾病,具有神经营养的作用[7-8]。此外,DHA 在治疗多发性骨髓瘤患者因硼替佐米引起的周围神经病变方面具有一定的预防作用[9]。因此,我们根据随机对照试验原则设计了一个安慰剂对照的随机、双盲临床试验,观察并分析 ω-3PUFAs 在防治结肠癌患者 XELOX 方案化疗所引起的周围神经毒性方面的作用,为 ω-3PUFAs 防治奥沙利铂所致周围神经毒性提供临床依据。

## 1 资料与方法

### 1.1 病例选择

纳入 2017 年 4 月至 2019 年 2 月浙江省肿瘤医院中西医结合科收治的结肠癌患者。

纳入标准:(1)经手术完全切除的高危Ⅱ期和Ⅲ期结肠癌患者;(2)晚期转移性结肠癌;(3)预期能完成 6 个 XELOX 化疗方案的结肠癌患者;(4)WHO PS 评分 0~1 分;(5)既往未使用任何其他可能引起神经毒性的化疗药物如奥沙利铂、顺铂、紫杉类药物等;(6)肝肾功能基本正常;(7)具有完整的病史记录及随访资料。本研究经医院伦理委员会批准[zjzlyy 伦理批件:IRB-2015-216 号(科)],均获患者知情同意。

排除标准:(1)所有包括具有化疗史、糖尿病、周围神经病变、骨髓抑制、心脏功能障碍、艾滋病毒、酗酒、甲状腺机能障碍和遗传周围神经病变相关疾病;(2)入组前 3 个月任何形式的营养补充(鱼油、维生素和矿物质)的患者。

脱落标准:治疗过程中,患者要求退出;依从性差,不能按研究设计进行治疗及检测的患者。

### 1.2 研究方法

共纳入 80 例结肠癌患者,采用随机信封法分为两组:治疗组(ω-3 PUFAs+化疗)和对照组(安慰剂+化疗)。

治疗组:在化疗当日起至第 6 个周期化疗结束期间,口服含 640mg ω-3 PUFAs 鱼油胶囊 1 颗,每日 3 次(浙江海力生有限公司生产)。对照组:化疗当日起至第 6 个周期化疗结束期间,口服等热卡(6kcal)的鱼油模拟安慰剂胶囊 1 颗,安慰剂是液态胶囊,内容物是食用油,每日 3 次(浙江海力生有限公司生产)。化疗方案:两组均接受 XELOX 方案化疗(奥沙利铂 130mg/m$^2$ 联合卡培他滨 1000mg/m$^2$),每 3 周重复 1 次,共 6 个周期。

### 1.3 神经毒性评价

#### 1.3.1 神经毒性分级标准

按照奥沙利铂神经毒性分级标准[10]评定(Table 1)。

#### 1.3.2 神经传导检测

使用基于 Nicolet/ VIASYS Viking Quest EMG 标准方法的肌电图机,对患者进行单侧(右侧)神经传导研究。测量胫神经、腓神经、尺神经的远端运动潜伏期(distal motor latency,DML),复合肌肉动作电位振幅(amplitude of compound muscle action potential,a-CMAP)和运动传导速度(motor conduction veloci-

**Table 1 Classification criteria for neurotoxicity**

| Level | Clinical presentation |
|---|---|
| 0 | None |
| Ⅰ | Paresthesia or dysesthesia[a],but does not affect function |
| Ⅱ | Paresthesia or dysesthesia[a],affects function, but not daily activities |
| Ⅲ | Paresthesia or dysesthesia[a],It is associated with pain and functional impairment,and affects daily activities |
| Ⅳ | Persistent paresthesia or sensory impairment leads to loss of function or life threatening |

a:Probably because of cold hands.

ty,MCV)作为运动传导评估;测量腓神经和尺神经的感觉动作电位(sensory action potential amplitude,a-SAP)和感觉传导速度(sensory conduction velocity,SCV)对感觉神经传导进行评价。

1.3.3 神经毒性评价时间

根据相关临床研究报道[11],课题组选取两组患者在化疗后1个月进行神经毒性评价;神经传导检测分别于化疗前及化疗后1个月进行检测。

**1.4** 统计学处理

全部资料数据输入计算机建立数据库,采用SPSS 19.0软件包进行数据分析。患者特征性比较采用卡方或Fisher's检验;两组间神经传导差异比较采用*t*检验。双侧检测。$P<0.05$为差异有统计学意义。

## 2 结 果

**2.1** 一般情况

80例患者中,共73例完成全部研究内容,脱落7例。其中治疗组有2例Ⅳ度骨髓抑制而暂停化疗;1例患者在1个疗程后不愿意继续退出。对照组有3例(2例Ⅳ度骨髓抑制、1例化疗后出现Ⅲ度肝功能异常而暂停化疗)退出;1例患者在2个疗程后不愿意继续而退出。脱落病例未纳入统计。两组患者在性别($\chi^2=0.130$,$P=0.719$)、年龄($\chi^2=0.674$,$P=0.412$)、分期($\chi^2=1.122$,$P=0.290$)、ECOG评分($\chi^2=0.019$,$P=0.892$)等资料分布均衡($P>0.05$)(Table 2)。

**2.2** 周围神经毒性疗效分析

与安慰剂组相比,两组的周围神经病变发生率存在显著性差异($\chi^2=43.975$,$P<0.001$)。ω-3 PUFAs组周围神经病变严重程度明显低于安慰剂组,差异具有统计学意义($\chi^2=47.768$,$P<0.001$)(Table 3)。

**2.3** 神经传导差异比较

治疗组与对照组化疗后腓肠神经的感觉动作电位(a-SAP)分别为(13.91±1.95)μV和(11.08±2.01)μV,差异具有统计学意义($P<0.001$)。其他神经传导研究数据比较无统计学差异(Table 4,5)。

**Table 2 Comparison of clinical features in two groups**

| Items | N | ω-3 PUFAs (n=37) | Placebo (n=36) | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Gender | | | | 0.130 | 0.719 |
| Male | 39 | 19 | 20 | | |
| Female | 34 | 18 | 16 | | |
| Age(years old) | | | | 0.674 | 0.412 |
| <65 | 36 | 20 | 16 | | |
| ≥65 | 37 | 17 | 20 | | |
| ECOG | | | | 0.019 | 0.892 |
| 2 | 31 | 16 | 15 | | |
| 3 | 42 | 21 | 21 | | |
| Clinical stage | | | | 1.122 | 0.290 |
| Ⅲ | 35 | 20 | 15 | | |
| Ⅳ | 38 | 17 | 21 | | |

**Table 3 Comparison of peripheral neuropathy in two groups**

| Group | N | 0 | Ⅰ | Ⅱ | Ⅲ | Ⅳ | Incidence | Severity of neuropathy |
|---|---|---|---|---|---|---|---|---|
| ω-3 PUFAs | 37 | 24 | 6 | 4 | 3 | 0 | 13(35.13%) | |
| Placebo | 36 | 10 | 10 | 7 | 5 | 4 | 26(72.22%) | |
| $\chi^2$ | | | | | | | 43.975 | 47.768 |
| *P* | | | | | | | 0.000 | 0.000 |

**Table 4 Motor nerve conduction measurements in two groups($\bar{x}\pm s$)**

| Items | Group | Pre-chemotherapy | Post-chemotherapy* | *P* |
|---|---|---|---|---|
| Peroneal nerve | | | | |
| DML(ms) | ω-3 PUFAs | 15.01±1.04 | 15.39±1.05 | 0.075 |
| | Placebo | 14.83±1.28 | 14.90±1.24 | |
| a-CMAP(mV) | ω-3 PUFAs | 6.98±1.17 | 6.61±1.28 | 0.090 |
| | Placebo | 6.32±1.00 | 6.12±1.14 | |
| MCV(m/s) | ω-3 PUFAs | 46.42±3.44 | 45.95±3.10 | 0.862 |
| | Placebo | 47.38±3.65 | 45.71±7.83 | |
| Ulnar nerve | | | | |
| DML(ms) | ω-3 PUFAs | 10.11±1.23 | 10.42±1.28 | 0.798 |
| | Placebo | 10.40±1.60 | 10.33±1.60 | |
| a-CMAP(mV) | ω-3 PUFAs | 17.49±2.14 | 16.54±1.98 | 0.466 |
| | Placebo | 16.42±1.70 | 16.22±1.72 | |
| MCV(m/s) | ω-3 PUFAs | 57.83±4.75 | 56.71±4.92 | 0.273 |
| | Placebo | 55.99±3.92 | 55.55±4.01 | |
| Tibial nerve | | | | |
| DML(ms) | ω-3 PUFAs | 16.77±1.32 | 17.34±1.19 | 0.160 |
| | Placebo | 16.57±1.20 | 16.96±1.14 | |
| a-CMAP(mV) | ω-3 PUFAs | 11.20±1.84 | 11.56±1.86 | 0.078 |
| | Placebo | 11.31±2.11 | 10.71±2.17 | |
| MCV(m/s) | ω-3 PUFAs | 46.61±2.10 | 46.15±2.07 | 0.348 |
| | Placebo | 46.87±4.85 | 46.97±4.90 | |

DML:distal motor latency;a-CMAP:amplitude of compound muscle action potential;MCV:motor cond uction velocity

**Table 5 Sensory nerve conduction measurements in two groups($\bar{x}\pm s$)**

| Items | Group | Pre-chemotherapy | Post-chemotherapy | *P* |
|---|---|---|---|---|
| Ulnar nerve | | | | |
| a-SAP(μV) | ω-3 PUFAs | 35.12±5.18 | 26.59±5.67 | 0.298 |
| | Placebo | 32.12±5.13 | 25.34±4.38 | |
| SCV(m/s) | ω-3 PUFAs | 57.14±5.29 | 56.14±5.24 | 0.239 |
| | Placebo | 55.16±5.21 | 54.68±5.21 | |
| Sural nerve | | | | |
| a-SAP(μV) | ω-3 PUFAs | 13.81±1.99 | 13.91±1.95 | 0.001 |
| | Placebo | 13.16±2.19 | 11.08±2.01 | |
| SCV(m/s) | ω-3 PUFAs | 54.62±6.54 | 55.25±5.98 | 0.315 |
| | Placebo | 54.46±4.23 | 54.02±4.28 | |

a-SAP:sensory action potential amplitude;SCV:sensory conduction velocity

## 3 讨 论

奥沙利铂是目前临床上结肠癌患者常用的化疗药物,能改善结直肠癌患者的预后,延长其生存时间[12-13],但由于奥沙利铂所致的神经毒性限制了药物剂量的使用[5]。奥沙利铂的神经毒性主要以周围神经毒性为主,包括急性周围神经毒性和慢性神经毒性[14-15]。急性周围神经毒性常发生于用药过程中,主要表现为迅速发作的对冷刺激敏感的末梢神经感觉异常,如肢端、口咽麻木或疼痛,部分可自行恢复。奥沙利铂的急性毒性是一种通道病,通过影响钠离子通道,从而增加感觉神经元的兴奋性,这是由于其代谢产物草酸盐所致。慢性周围神经毒性是多周期使用奥沙利铂后出现的迟发型周围神经病变,表现为深浅感觉缺失、共济失调,随后可出现书写及扣纽扣等精细动作困难,严重影响生活质量,也是导致患者减量或者停药的原因。与急性神经毒性相似,慢性周围神经毒性通过影响钠离子通道,加剧神经细胞离子转运和能量代谢障碍,超出代偿限制,造成轴浆运输衰竭,神经细胞体缺乏反向运输带来的神经生长因子,周围神经纤维缺乏轴浆运输的促神经发育、修复作用,最终不可避免地出现变性。

目前,临床上一般通过停药方式来恢复,或者使用维生素类、核苷酸类、钙剂、镁剂、还原型谷胱甘肽等药物来治疗。这些药物通过提高蛋氨酸合成酶的活性,促进髓鞘的主要结构磷脂酰胆碱合成,恢复因化疗受损的髓鞘的功能,从而减轻化疗的神经毒性[16]。但是上述诸多治疗方法均需较长的治疗周期,且临床疗效欠佳,其具体作用机制也不明了,亦缺乏较大规模的临床研究。

ω-3 PUFAs 作为一种长链脂肪酸,对肠癌、肺癌、乳腺癌、卵巢癌等有抗肿瘤作用[17-18],且能有效地提高患者的机体免疫[19]。此外,研究证实 ω-3 PUFAs 具有营养保护周围神经的作用。Silva 等[20]建立部分坐骨神经结扎诱导神经性疼痛模型小鼠,通过补充鱼油(EPA/DHA),发现鱼油能促进坐骨神经中 GAP43 表达增加和髓纤维总数的增加,抑制神经炎症活性,从而保护神经损伤。同时,相关研究均证实 ω-3 PUFAs 可通过减少神经炎症及氧化应激等途径,减轻神经性疼痛[21-22]。此外,在化疗药物(多柔比星)引起的抑郁样行为及神经毒性模型大鼠中,发现 DHA 能抑制 IL-1β,IL-6 及 TNF-α 等炎症因子,同时能抑制 NF-κB 及 iNOS 信号通路,从而起到保护神经作用[23]。

本研究采用双盲安慰剂随机对照研究,观察 ω-3 PUFAs 对结肠癌患者因奥沙利铂化疗引起的周围神经病变的治疗和预防作用,结果显示,两组患者的周围神经病变发生率有显著性差异。治疗组 64.87%患者没有出现周围神经毒性,而对照组仅有 27.78%的患者未发生周围神经毒性。同时,在治疗组中发生严重周围神经毒性的患者明显少于对照组,结果表明 ω-3 PUFAs 能降低奥沙利铂导致的周围神经毒性发生发展,起到预防及治疗的作用。此外,在神经传导方面,两组腓肠神经感觉动作电位(a-SAP)存在显著性差异。在 XELOX 方案化疗后,对照组的感觉动作电位明显下降,表明 ω-3 PUFAs 抑制了腓肠神经感觉动作电位的下降,从而起到保护周围神经的作用。

综上所述,在结肠癌患者中,ω-3 PUFAs 能减轻 XELOX 方案化疗所致的外周神经毒性,表明 ω-3 PUFAs 在防治奥沙利铂所致的周围神经毒性方面具有一定的作用;但是,由于其作用机制不明,还需进一步进行相关机制的研究。

## 参考文献:

[1] Bray F,Ferlay J,Soerjomataram I,et al. Global cancer statistics 2018:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin,2018,68(6):394-424.

[2] Benson AR,Venook AP,Cederquist L,et al. Colon cancer,

version 1.2017,NCCN clinical practice guidelines in oncology[J]. J Natl Compr Canc Netw,2017,15(3):370–398.

[3] Shahnam A,Ridha Z,Wiese MD,et al. Pharmacogenetic and ethnicity influence on oxaliplatin therapy for colorectal cancer:a meta-analysis[J]. Pharmacogenomics,2016,17(15):1725–1732.

[4] Guo Y,Xiong BH,Zhang T,et al. XELOX vs. FOLFOX in metastatic colorectal cancer:an updated meta-analysis[J]. Cancer Invest,2016,34(2):94–104.

[5] Griffith KA,Zhu S,Johantgen M,et al. Oxaliplatin-induced peripheral neuropathy and identification of unique severity groups in colorectal cancer[J]. J Pain Symptom Manage,2017,54(5):701–706.

[6] Beijers AJ,Mols F,Vreugdenhil G. A systematic review on chronic oxaliplatin-induced peripheral neuropathy and the relation with oxaliplatin administration[J]. Support Care Cancer,2014,22(7):1999–2007.

[7] Zhang YP,Brown RE,Zhang PC,et al. DHA,EPA and their combination at various ratios differently modulated abeta25-35-induced neurotoxicity in SH-SY5Y cells[J]. Prostaglandins Leukot Essent Fatty Acids,2018,136:85–94.

[8] Lorente-Cebrian S,Costa AG,Navas-Carretero S,et al. An update on the role of omega-3 fatty acids on inflammatory and degenerative diseases[J]. J Physiol Biochem,2015,71(2):341–349.

[9] Maschio M,Zarabla A,Maialetti A,et al. Prevention of bortezomib-related peripheral neuropathy with docosahexaenoic acid and alpha-lipoic acid in patients with multiple myeloma:preliminary data [J]. Integr Cancer Ther,2018,17(4):1115–1124.

[10] Lei Y,Wen C. Randomized controlled clinical observation of qiteng tongbi fumigation lotion combined with ganglioside to prevent neurotoxicity induced by mFOLFOX6 chemotherapy[J]. Journal of Chongqing Medical University,2019,44(7):938–943.[叶磊,陈文. 芪藤通痹熏洗液联合神经节苷脂预防 mFOLFOX6 方案化疗所致神经毒性的随机、对照临床观察[J]. 重庆医科大学学报,2019,44(7):938–943.]

[11] Ghoreishi Z,Esfahani A,Djazayeri A,et al. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy:a randomized double-blind placebo controlled trial[J]. BMC Cancer,2012,12:355.

[12] Leal F,Ferreira FP,Sasse AD. FOLFOXIRI regimen for metastatic colorectal cancer:a systematic review and meta-analysis[J]. Clin Colorectal Cancer,2017,16(4):405–409.

[13] Wardhani Y,Hutajulu SH,Ferianti VW,et al. Effects of oxaliplatin-containing adjuvant chemotherapy on short-term survival of patients with colon cancer in Dr. Sardjito Hospital,Yogyakarta,Indonesia [J]. J Gastrointest Oncol,2019,10(2):226–234.

[14] Argyriou AA,Cavaletti G,Briani C,et al. Clinical pattern and associations of oxaliplatin acute neurotoxicity:a prospective study in 170 patients with colorectal cancer[J]. Cancer,2013,119(2):438–444.

[15] Raphael MJ,Fischer HD,Fung K,et al. Neurotoxicity outcomes in a population-based cohort of elderly patients treated with adjuvant oxaliplatin for colorectal cancer[J]. Clin Colorectal Cancer,2017,16(4):397–404.

[16] Wen F,Zhou Y,Wang W,et al. Ca/Mg infusions for the prevention of oxaliplatin-related neurotoxicity in patients with colorectal cancer:a meta-analysis [J]. Ann Oncol,2013,24(1):171–178.

[17] Zhang K,Hu Z,Qi H,et al. G-protein-coupled receptors mediate omega-3 PUFAs-inhibited colorectal cancer by activating the Hippo pathway[J]. Oncotarget,2016,7(36):58315–58330.

[18] Wang W,Zhu J,Lyu F,et al. Omega-3 polyunsaturated fatty acids-derived lipid metabolites on angiogenesis,inflammation and cancer[J]. Prostaglandins Other Lipid Mediat,2014,113–115:13–20.

[19] Ma CJ,Wu JM,Tsai HL,et al. Prospective double-blind randomized study on the efficacy and safety of an n-3 fatty acid enriched intravenous fat emulsion in postsurgical gastric and colorectal cancer patients[J]. Nutr J,2015,14:9.

[20] Silva RV,Oliveira JT,Santos B,et al. Long-chain omega-3 fatty acids supplementation accelerates nerve regeneration and prevents neuropathic pain behavior in mice [J]. Front Pharmacol,2017,8:723.

[21] Galan-Arriero I,Serrano-Munoz D,Gomez-Soriano J,et al. The role of omega-3 and omega-9 fatty acids for the treatment of neuropathic pain after neurotrauma [J]. Biochim Biophys Acta Biomembr,2017,1859(9 Pt B):1629–1635.

[22] Huang CT,Tsai YJ. Docosahexaenoic acid confers analgesic effects after median nerve injury via inhibition of c-Jun N-terminal kinase activation in microglia[J]. J Nutr Biochem,2016,29:97–106.

[23] Wu YQ,Dang RL,Tang MM,et al. Long chain omega-3 polyunsaturated fatty acid supplementation alleviates doxorubicin-induced depressive-like behaviors and neurotoxicity in rats:involvement of oxidative stress and neuroinflammation[J]. Nutrients,2016,8(4):243.