The antimanic-like effects of andrographolide and quercetin

VALORIZATION

Despite the numerous pharmacological options for bipolar disorder (BD), treatment still shows inadequate response in acute manic or depressive episodes or in long-term preventive maintenance treatment (Gitlin, 2006). Established first-line treatments include lithium, valproate and second-generation antipsychotics in acute mania, and lithium and valproate for maintenance treatment, as well as anticonvulsants. Combining multiple agents is the most commonly used clinical strategy, especially with antidepressants (López-Muñoz et al., 2018; Gitlin, 2006). Common adverse effects that result from the use of these drugs include weight gain, akathisia, nausea, vomiting, somnolence, tremors, dizziness, asthenia and blood dyscrasias, among many others (Bai et al., 2019; López-Muñoz et al., 2018). These aspects, such as low self-efficacy for medication-taking behavior, fear of dependence on medications, concern about medication adverse effects affect treatment adherence in BD (Levin et al., 2020; Levin et al., 2016; Chang et al., 2015; Devulapalli et al., 2010).

In this perspective, the research for new alternative drugs is relevant. We investigated the possible antimanic-like effects of andrographolide (ANDRO) and quercetin. We hypothesized that ANDRO could possess antimanic-like properties as it shares common mechanisms of action as the mood stabilizer lithium, for instance, inhibitory activity over the enzyme glycogen synthase kinase 3 beta (GSK3β) and antioxidant properties. We also hypothesized that the flavonoid quercetin could exert antimanic-like properties as it also has similar mechanisms of action as lithium, such as inhibitory activity over protein kinase C (PKC) and antioxidant effects.

ANDRO is already sold and consumed worldwide as dietary supplement as *Andrographis paniculata* pills (powdered plant) or Kalmegh pills, mainly for its anti-inflammatory and antioxidant properties (Kataky and Handique, 2010). Safety has been widely tested preclinically. Bothiraja et al. (2012) showed that up to 5 g/kg or 500 mg/kg oral doses of ANDRO given daily for up to 14 days and 21 days, respectively, had no observable adverse effects in rats. Handa and Sharma (1990) showed that the LD_{50} of ANDRO given via intraperitoneal injection to mice is 11.46 g/kg. Prakash and Manavalan (2011) showed that the acute administration of 2000 mg/kg ANDRO p.o. in mice did not alter body or liver weight, kidney and heart. It neither altered creatinine,

total cholesterol or blood sugar levels, nor hematological parameters, such as platelet counts, hemoglobin or red/white blood cells of mice treated with ANDRO when compared to the control group. Al Batran et al. (2013) showed that acute oral administration of 500 mg/kg ANDRO did not induce toxic effects in the liver or kidney in rats. These studies show that ANDRO appears to be relatively safe, and for this reason, there is an increasing interest in its therapeutic use (Lu et al., 2019; Tan et al., 2017).

In addition, scientific research involving ANDRO does not rely solely upon pre-clinical tests, but several clinical studies have already been performed and are still being developed. In a randomized, double-blind, placebo-controlled trial, the therapeutic efficacy of tablets of *A. paniculata* extract (170 mg of *A. paniculata* containing 85 mg of ANDRO) was evaluated in subjects with relapsing-remitting multiple sclerosis receiving interferon therapy significantly improved multiple sclerosis-associated fatigue (following the Fatigue Severity Scores), in 44% compared to the placebo group (Bertoglio et al., 2016). A phase II randomized double-blind placebo-controlled clinical study for the evaluation of *A. paniculata* oral tablets in patients with multiple sclerosis was completed in 2015 (NCT02280876), but the results are yet to be published. Thus, there are great perspectives for the research involving ANDRO and its therapeutic effects.

Quercetin is also taken as a dietary supplement as quercetin pills, due to its antioxidant properties (Vida et al., 2019). This flavonoid is widely distributed in nature in plants and vegetables as quercetin glycosides, while dietary supplements usually contain quercetin in its free form, as aglycones (Andres et al., 2017). In dietary supplements, recommended daily doses of quercetin aglycones can range up to 1000 mg (Andres et al., 2017). Studies show that no adverse effects were reported by volunteers after repeated daily intake of 500 mg quercetin for 4-8 weeks (Javadi et al., 2017), 730 mg quercetin for 4 weeks (Edwards et al., 2007), or 1000 mg for 5 days to 12 weeks (Rezvan et al., 2017), showing the safety in the administration or intake of quercetin. Ferry et al. (1996) showed that 945 mg/m² intravenous quercetin injection was still a safe dose of quercetin, demonstrating its safety, although studies suggest that excessive consumption of quercetin, above the recommended daily intake, can lead to nephrotoxicity and carcinogenesis (Singh et al., 2010; Dunnick and Hailey, 1992).

Clinical trials are in course to test the therapeutic effects of quercetin. A randomized double-blind placebo-controlled trial has shown that the combination of quercetin (500, 1000 or 2000 mg), vitamin C (350 mg) and niacin (10 mg) is beneficial for patients with chronic obstructive pulmonary disease (NCT01708278). Another randomized double-blind placebo-controlled clinical study to evaluate the effects of quercetin on sarcoidosis is taking place at Maastricht University, the Netherlands, where the antioxidant and inflammatory status of the participants is analyzed after 24 h from taking 1000 mg of quercetin (NCT00402623). Another research group is evaluating the effects of dietary supplement with luteolin (100 mg/capsule), quercetin (70 mg/capsule) and rutin (30 mg/capsule) on 50 children with autism spectrum disorders (NCT01847521). This shows a future perspective in the employment of quercetin as a drug in the management of various health problems.

BD patients have increased risk of many general-medical disorders, with increased morbidity, disability and diminished longevity (Baldessarini et al., 2020). BD patients have more adverse clinical outcomes and diminished life-expectancy, with all-cause mortality up to 15-times above general population rates (Ösby et al., 2018; Staudt-Hansen et al., 2019). Thus, it is very important to continue the research for new antimanic drugs that can be included in the pharmacological arsenal for the management of BD. Actually, our studies showed that ANDRO and quercetin exert antimanic-like effects and are promising candidates for further development and testing of new antimania drugs with a safe therapeutic window.