Herbal products and antidepressants: a safe combination or a risky mix?

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One in five adults in England has a common mental health condition, most commonly Generalised Anxiety Disorder (GAD) (7.5%) and depression (3.8%), and these are most frequently treated with prescribed medication (51.8% and 46.7%, respectively). Surveys estimate that concurrent use of herbal products and medication for psychological conditions ranges from 12-27.5% [1,2]. This raises safety concerns – for example, St John's Wort is contraindicated alongside selective serotonin reuptake inhibitors (SSRIs) due to similar mechanisms that increase the risk for serotonin syndrome. However, other herb-drug safety data is generally limited, and providing further evidence on this is vital for patient and clinician decision making.

We recently reviewed over-the-counter (OTC) products for anxiety, depression and insomnia in all age groups of adults and older adults [3–6]. Review searches were carried out in MEDLINE, Embase, PsycINFO, AMED, and CENTRAL (inception-Dec 2022) and included 404 randomised controlled trials (RCTs) of herbal products, dietary supplements, medications and homeopathic products, administered to adults for ≥1 week with symptoms or a diagnosis of depression, anxiety and/or insomnia. We found a wide range of products were tested. This letter reports on a closer analysis of the safety of herbal products, specifically those that were tested as adjunct therapies to prescribed antidepressant treatment compared a control treatment plus the antidepressant, and reported upon adverse events.

Out of the 163 herbal product RCTs, 17 were evaluated as adjuncts to antidepressants and reported data regarding adverse events (Table 1). Most studies were in people with a depression diagnosis (n=10) or anxiety diagnosis (n=4). Two were in people with a health condition plus depressive symptoms and one was in people with mild-moderate depressive symptoms.

Herbal products assessed included saffron/crocin (n=4) [7–10], curcumin (n=2) [11,12], and one each of rhodiola [13], cinnamon [14], black seed [15], passionflower [16], Echium [17], lavender [18], rosemary [19], ashwagandha [20], gingko [21] and St John's Wort [22]. Two combination

products were included (saffron, St John's Wort, cinnamon and grape juice [23]) and saffron plus curcumin [12]. Duration of use was 4-12 weeks. Most products were administered alongside SSRIs (n=13), reflecting current prescribing trends, mainly sertraline (n=5), with a small number of other drug types. Two studies assessed adjunctive treatment alongside usual antidepressants (taken by 42-64% patients [12]) or all patients [10]. Eleven studies reported that there were no serious adverse events (SAEs), whilst six discussed only adverse events (AEs), implying but not clearly stating a lack of SAEs.

Saffron and crocin (an extract from saffron) showed few safety issues, with no significant differences in AEs adjunctively to fluoxetine [8], mixed SSRIs [9] and mixed antidepressants [10] at 28-30mg/day. Where details were reported [7,9], these were mild (see Table 1). At higher doses (450mg/day), there were mild AEs alongside sertraline but placebo group AEs were not reported [7]. Curcumin (1000mg/day) alongside escitalopram produced mild nausea (frequency not reported) but otherwise no safety issues compared to placebo [11]. Alongside mixed antidepressants in a four-arm trial, there were no differences according to dosage or with a saffron-curcumin product, apart from high doses (1000mg/day) producing a higher frequency of diarrhoea [12].

Rhodiola and gingko appeared to have protective effects. Significantly fewer rhodiola patients reported AEs alongside sertraline than placebo, particularly at higher doses [13], whilst fewer AEs (significance not reported) occurred from gingko alongside venlafaxine than venlafaxine alone [21]. Similarly, alongside a combination of mixed tricyclic antidepressants, St John's Wort showed better quality sleep, fewer GI complications and increased energy. Photosensitivity was noted in three patients but managed using sunscreen [22].

Alongside sertraline, no complications were reported for black seed [15]. Cinnamon capsules and passionflower drops showed no significant differences in AE frequency vs placebo [14,16], but nausea and dizziness was higher in the passionflower group [16]. Echium plus fluoxetine

showed no significant differences compared to placebo, with the most common side effect being headache [17]. Alongside citalopram, lavender tea showed no significant differences in side effects vs citalopram alone, although nausea was more common in the lavender group, dry mouth in the citalopram group and confusion was common in both [18]. A combination product (saffron, St John's Wort, cinnamon and grape juice syrup) showed no serious adverse events alongside SSRIs maintained at a stable dose, with individual AEs not reported [23].

Alongside mixed SSRIs, ashwagandha showed no significant differences in side effects vs placebo, with only rare ones reported [20]. Rosemary however showed significantly higher rates of heart burn and increased memory alongside mixed SSRIs, and non-significantly higher nausea, constipation and drowsiness but lower levels of diarrhoea [19].

This analysis is limited by the small subset of studies that reported safety data, and even these were reported in variable detail. Trials mainly had small sample sizes and are likely underpowered for detecting AE differences. In a few studies antidepressants were used by the majority, but not all, of the sample. Reporting of manufacturing and quality control procedures was variable – in cases of safety it is essential this is clearly reported to ensure that product safety (or lack of) is not due to adulteration, poor quality or a lack of active metabolites or marker compounds, particularly given that many herbal products are not regulated as medicines [24].

Most products evaluated alongside antidepressants in this analysis showed few concerns regarding interactions, and some products may even mitigate antidepressant side effects. Studies need to assess longer term usage and more clearly report AE frequencies and types in both arms. Authors are also encouraged to follow the ConPhyMP reporting checklist [25] to report sourcing, processing, composition and quality assurance of plant extracts, to better inform future safety and effectiveness studies.

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