Citrus aurantium – beware of the bitter orange

To the Editor: The interesting case report regarding a young man who presented with a myocardial infarction after the use of a synephrine-containing substance[1] raises a number of issues.

The hypothesis that the infarction might have been caused by coronary spasm followed by thrombosis may be supported by a similar case of a 28-year-old man who developed a myocardial infarct after abusing synephrine tablets.[2] Many patients use complementary and alternative medicines (CAMs) in conjunction with their prescribed medicines – and up to 72% of users do not inform their treating physician accordingly.[3,4] With the narrow therapeutic window of many commonly used medicines, the potential interactions and adverse effects when used with CAMs should not be underestimated. In this particular context, *Citrus aurantium* (Seville or bitter orange) is found in a number of foodstuffs, including marmalade, beer (Belgian Orange Muscat) and some teas, and in over-the-counter weight-loss products. In some countries (e.g. Iran, Mexico), the dried or ripe fruit form part of local dietary traditions.

In addition to the mechanisms mentioned by the authors, in which the use of *C. aurantium* could lead to cardiovascular side-effects, is the effect on drug metabolism. *C. aurantium*, grapefruit (*C. paradisi*) and pomelo (*C. maximi*) contain a number of flavonoids including 6′,7′-dihydroxybergamottin, which is used to selectively block the intestinal cytochrome P450 isoenzyme, CYP3A4, in bioavailability studies.[5] *C. aurantium* also contains a furocoumarin (bergapten) that inhibits CYP3A4.[6] Since about a quarter of pharmaceuticals are metabolised by the CYP3A4 system (e.g. warfarin, felodipine, indinavir, simvastatin), and an inhibitory effect on this system could lead to increased serum drug levels of drugs metabolised by CYP3A4, a great potential for adverse interactions exists.[5] The potential negative interaction of *C. aurantium* has been noted by some drug manufacturers, where its concomitant use is contraindicated with agents such as imatinib and nilotinib, which are used in the treatment of chronic myeloid leukaemia.

A greater awareness of the potential danger of *C. aurantium* and other CAMs, when used in combination with other drugs, should contribute to increased patient safety. We therefore believe that it is reasonable to suggest that pharmaceutical manufacturers, pharmacists and prescribers take potential drug-CAM interactions into account, especially with the preparation of package inserts and when writing prescriptions. The public should be educated to be aware of the injudicious use of CAMs and that not informing their doctors of their use could have dire consequences.

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