medical sciences forum

MDPI

Proceeding Paper

Nutraceuticals for Smart Aging and Potential Drug Interactions †

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† Presented at the 5th International Congress of CiiEM—Reducing Inequalities in Health and Society, Online, 16–18 June 2021.

Abstract: The use of nutraceuticals as cognitive enhancers is on the rise and may be especially problematic in polymedicated older patients. The potential of interaction of these products with drugs commonly prescribed to this age group is evaluated in this work, by identification of mutual targets (enzymes, transporters and receptors).

Keywords: nutraceuticals; aging; cognitive enhancement; drug interactions

Citation: Auxtero, M.D.; Abade, M.; Chalante, S.; Silva, B.; Fernandes, A.I. Nutraceuticals for Smart Aging and Potential Drug Interactions . *Med. Sci. Forum* **2021**, *5*, 4. https://doi.org/10.3390/msf2021005004

Academic Editors: Helena Barroso and Cidália Castro

Published: 9 July 2021

1. Introduction

Nutraceuticals are increasingly being used in the management of age-related cognitive disorders [1,2] due to the combination of neuroprotection and/or neurotransmission. However, these products are not exempt from adverse effects and pharmacological interactions, presenting a special risk in older, multimorbid and polymedicated individuals. Understanding pharmacokinetic (PK) and pharmacodynamic (PD) interactions allows anticipation of adverse drug reactions and therapeutic failure.

This study reviews the mechanism of action and interactions between bioactive compounds used for cognitive enhancement and representative drugs, of ten different pharmacotherapeutic classes, usually prescribed to older patients.

2. Materials and Methods

The composition of 25 common nutraceuticals used for cognitive enhancement of adults over 50 years was evaluated. Four bioactive molecules (bacoside A (BA), salidroside (SD), deanol (DE) and homotaurine (HT)) and two plant extracts (*Bacopa monnieri* (BM) and *Rodhiola rosea* (RR)) were selected for further characterization. Propranolol (Pr), alprazolam (Al), sertraline (Se), metformin (Mt), diclofenac (Di), atorvastatin (At), tadalafil (Ta), memantine (Me), piracetam (Pi) and clopidogrel (Cl) were the drugs selected. A full PK/PD profile was obtained for each drug, focusing on the role of multiple enzymes, transporters and receptors, and identifying common targets of the bioactive molecules, as a measure of potential drug/nutraceutical interaction. Databases such as Cochrane Library, Science Direct, PubMed, MedlinePlus, WebMD and Drug Bank were consulted.

3. Results and Discussion

HT is the less problematic of the bioactives studied since it only interacts with NMDA receptor, as an antagonist. Both RR and BA (bioactive of BM) show inhibitory effects on monoamine oxidase A and B (MAO A and B). Hence, nutraceuticals containing any of the two bioactives (and tyramine rich food) should be avoided whenever therapeutics include selective serotonin reuptake inhibitors (e.g., Se, a MAO substrate) and blood pressure medication (e.g., Pr, a MAO A inhibitor). P-glycoprotein (P-gp) is a membrane efflux

transporter, influencing oral bioavailability of its substrates, such as Pr, Se, Di, At, Ta and Cl. Since P-gp is inhibited by BM and SD, the concomitant use of those drugs may greatly increase their oral bioavailability. Similar to RR and BA, DE showed inhibitory capacity for several cytochrome P450 enzymes, whereas SD proved to be an inducer (Table 1). CYP3A4 is responsible for the metabolism of 70% of the drugs considered and it is inhibited by BA and RR, resulting in decreased plasma clearance of those drugs and increased risk of toxicity. It is of the utmost relevance to fully understand these interactions, in order to prevent side effects, especially with 'High-Alert Medications' (HAM) (60% of those studied) and narrow therapeutic index drugs.

Table 1. Targets of potential interactions between drugs and bioactive molecules (or plant extracts).

Drug	Enzyme (E)/Transporter (T)/Receptor (R)										
	CYP						MAO		P-gp	MRP1	NMDA
	1A2	3A4	2C9	2B6	2D6	2C19	A	B			
Al ▲	-	S BA * RR *	S BA * RR * SD *	-	-	-	-	-	-	-	-
At ▲	-	S BA * RR *	↓BA * RR * SD •	↑ SD **	↓ DE *	↓ BA * DE *	-	-	S↓ BM * SD *	S SD *	-
Cl ▲	S BA * RR * SD • DE *	S BA * RR *	S ↓BA * RR * D •	S ↓ SD •	-	S BA * DE *	-	-	S BM * SD *	-	-
Di ▲	S BA * RR * SD • DE *	S ↓ BA * RR *	S ↓ BA * RR * SD •	S SD •	-	S BA * DE *	-	-	↑ BM * SD *	↓ SD *	-
Me	-	-	-	↓ SD •	-	↓ BA * DE *	-	-	-	-	AN HT ■
Mt ▲/Pi	-	-	-	-	-	-	-	-	-	-	-
Pr ▲	S BA *RR * SD • DE *	S BA * RR *	-	-	S ↓ DE *	S BA * DE *	↓ BA * RR *	-	S BM * SD *	-	-
Se	-	S BA * RR *	↓ BA * RR * SD •	S ↓ SD •	S ↓ DE *	S ↓ BA * DE *	S BA * RR *	S BA * RR *	S ↓ BM * SD *	-	-
Ta	-	S BA * RR *	-	-	-	-	-	-	S BM * SD *	-	-

S: drug is substrate of E, T or R; ↓: drug is inhibitor of E, T or R; ↑: drug is inducer of E, T or R; AN: drug is antagonist of R; * inhibitor of E, T or R; • inducer of E, T or R; ■ R antagonist; ▲ HAM.

Bioactives of botanical origin are more likely to lead to interaction, as expressed by the higher the number of mutual targets affected (up to eight for RR/SD with Di). BA/BM inhibit four main CYP enzymes (2C19, 2C9, 1A2 and 3A4), P-gP and MAO (A/B), thus potentially increasing plasma levels of 70% of the drugs considered (Pr, Al, Se, Di, At, Me, Ta and Cl). RR/BA interact with MAO inhibitors, CYP2C9 substrates and serotonin reuptake inhibitors.

Results confirm that the co-administration of nutraceuticals and drugs can alter PK/PD parameters, resulting in side effects or therapeutic failure. Systematic monitoring of the addition of such products, often erroneously mistaken as medicines, to the therapeutic regimen of polymedicated older patients is especially important.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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