Common interactions between drugs and herbal supplements used in alternative medicine

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COMMON INTERACTIONS BETWEEN DRUGS AND HERBAL SUPPLEMENTS USED IN ALTERNATIVE MEDICINE

Graduate thesis

Zagreb, 2018.

This graduate thesis was made at the Department of Internal Medicine, Unit of Clinical Pharmacology, mentored by Prof. dr. sc. Robert Likić and was submitted for evaluation in the academic year 2017/2018.

Abbreviations

ADR – Adverse Drug Reaction

CAM – Complementary and alternative medicine

OTC – Over the counter

FDA – Food and Drug Administration

GMP - good manufacturing practices

P-gp – P-glycoprotein

Contents

1. Summary

Dietary supplements are formulations which contain pharmacologically active phytochemicals. In recent years, the use of alternative and complementary medicine (CAM) has increased significantly. As herbal supplement manufacturers aren't obligated to undergo extensive regulation, the possibility of herb-drug interactions is increased when compared with the likelihood of interactions between two prescription drugs. There is a common misconception that because herbal supplements are derived from plants, they are safer because they are ″natural″. Commonly, it is difficult to determine the offending substance in herb-drug interactions, particularly when it takes place in patients who are prescribed several different medications.

Here, we will review the most common herbs involved in herb-drug interactions, as well as the results of search criteria involving these interactions.

2. Sažetak

Dodaci prehrani mogu sadržavati farmakološki aktivne tvari. U posljednjih nekoliko godina, korištenje alternativne medicine, biljnih lijekova, i dodataka prehrani se znatno povećalo. Budući da dodaci prehrani nisu pod nadzorom proizvodnje, mogućnost interakcija između dodataka i lijekova je znatno povećana naspram interakcija između lijekova. Postoji česta zabluda da su biljni lijekovi sigurni zbog toga što su proizvedeni od takozvanih ″prirodnih″ biljaka.

Često je teško doprijeti do tvari koja je dovela do interakcije u pitanju, pogotovo kad je polifarmacija u pitanju.

U ovom radu će se propitati najčešći preparati uključeni u česte interakcije između biljnih preparata i lijekova, kao i rezultati internet-tražilica koje uključuju te interakcije.

3. Preface

3.1 Introduction

In recent years, the use of alternative and complementary medicine (CAM) has increased significantly. With the advancement of medicine and the fields it encompasses, new treatments have been developed, and previous treatments have improved substantially. In some cases, modern medicine falls short of expectations and patients become dissatisfied. In an effort to improve their health, they seek alternative treatment. In other cases, patients simply wish to improve their health with supplements.

Unfortunately, this carries with it the possibility of interactions between prescribed drugs and over-the-counter supplements.

Dietary supplements are defined by the Dietary Supplement and Health Education Act (DSHEA) of 1994 (1) and include such products as herbals, vitamins, minerals, sports nutrition supplements, weight management products, specialty supplements and other oral dosage forms intended to supplement the diet (2).

Dietary supplements are formulations which may contain pharmacologically active phytochemicals. These are generally extracted from a variety of plant sources, and can be obtained in various formulations. Most commonly, they are purchased as extracts in capsules, but are also available as powders, teas, and other ingestible forms. Some can be found as the active ingredients in nutrition bars or sports performance drinks.

Herbal supplements usually have many active phytochemical constituents. Therefore, the possibility of interactions is increased when compared with the likelihood of interactions between two prescription drugs (3). Presently, most herbal drug interactions are documented as case series or individual case reports (4).

There is a common misconception that because herbal supplements are derived from plants, they are safer because they are ″natural″. Unfortunately, the Food and Drug Administration (FDA) does not regulate dietary supplements in the same was it regulates prescription medications and

food additives. Dietary supplement manufacturers are not obliged to follow good manufacturing practices (GMP) as are pharmacological companies or food manufacturers. Consequently, the products they offer have no reliable levels of their active ingredients or reported additional active ingredients which may be a manufacturing by-product and/or impurity.

The exact pharmacological composition of herbal supplements may fluctuate depending on the time of the year the plant was harvested in, the ratio of different plant components, and the conditions the plants were grown in. Additionally, when drug-supplement interactions are mentioned in case reports, it must be noted that these interactions may be a result of additives, inactive ingredients, or trace amounts of other herbs.

Testing of the quality of more than 1200 dietary supplement products by the independent laboratory ConsumerLab.com found that 1 in 4 dietary supplement products lacked the labeled ingredients or had other serious problems such as unlisted ingredients or contaminants (5).

There are currently approximately 20,000 available herbal supplements available on the US market. (6). The top 10 most commonly used herbs in the United States are Echinacea, Ginseng, Gingko biloba, Garlic, St. John's wort, Peppermint, Ginger, Soy, Chamomile, and Kava kava. Five of the top ten have demonstrated significant evidence showing pharmacological efficacy for certain indications. Those include Ginkgo, Garlic, St. John's wort, Soy, and Kava. However, even for these commonly used herbs, the scientific evidence often suffers from poor methodology, inconsistent outcome measures, different preparations of the herb, and conflicting results (7).

It is commonly difficult to determine the offending substance in herb-drug interactions, particularly when it takes place in patients who are prescribed several different medications. Polypharmacy is emerging as an increasingly important issue with the aging of the world population. It is estimated that by the year 2050 the population of people aged more or equal to 60 years will double and around 400 million people will be more or equal to 80 years of age (8).

This change in demographics has been enabled with advances in medical technology, diagnostics, and treatment. Furthermore, with increasing complexity of therapy comes increased complexity of therapy management. Older adults are the biggest consumers of prescription and over-the-counter (OTC) medicines (9). As healthcare systems suffer larger patient loads, increased hospitalizations,

and protracted hospital stays due to ADRs, possible herb–drug interactions are significant medical and financial concerns (10).

Patients are frequently under the impression that herbal supplements are entirely harmless. In fact, most do not even consider herbal supplements as possible culprits when faced with an ADR. Additionally, the ADR might be considered to be a novel disease process necessitating further therapy with prescriptions intended to mitigate new symptoms. This might further increase the number of medications the patient is taking, leading to an even higher incidence of ADRs.

The first major concern of herbal drug interactions was recognized in 1989 when grapefruit juice was reported to increase the blood concentration of felodipine, an anti-hypertensive calcium channel antagonist (11).

Factors which increase the risk of potential important herb-drug interactions are similar to those affecting prescription medications. Those are demographic characteristics (such as extremes of age, frailty, female gender, mental status, co-morbidities, and hereditary features), pharmacological factors (polypharmacy, adjustments in dosage or addition of new medications, narrow therapeutic windows, and limitations in elimination pathways) (12).

3.2 Herb-Drug Interactions – Definition

Herb-drug interactions occur as a result of the same principles as with interactions between prescription medications. These are the result of the same pharmacokinetic and pharmacodynamic interactions. The interactions presently identified involving prescription drugs and herbs or herbal dietary supplements suggest that a number of herbs, most notably St. John's wort, can alter the plasma concentration of a number of common drugs metabolized by CYP, and/or are transported by P-gp (13). P-gp is expressed in the intestine, liver, and kidney; it performs an important role in the absorption, distribution, or excretion of drugs (14).

4. Common Herb-Drug Interactions

4.1 St. John's wort

St. John's wort contains hyperforin, which acts to induce the cytochrome P450 3A4 (CYP3A4) system, which metabolizes a number of drugs including protease inhibitors, cyclosporine, oral contraceptives, irinotecan, warfarin, and digoxin. Failure of antiretroviral therapy, transplant rejection, and contraceptive failure have been reported. In addition, St. John's wort may produce the serotonin syndrome when taken with other serotonergic medications (15).

Likewise, treatment failures with a wide variety of agents including anticoagulants, antiretrovirals, antifungals, immunosuppressive agents, narcotics, digoxin, and hormonal contraceptives have been associated with the concomitant use of St. John's wort due to significant induction of CYP 1A2, 2C19, 2C9, and 3A4, as well as intestinal P-glycoprotein/MDR-1 drug transporters (16).

4.2 Gingko biloba

Ginkgo (Ginkgo biloba leaves) is an herb used mainly to treat or prevent memory issues, as well as tinnitus and peripheral vascular disease. Its active ingredients ginkgolide, bilobalides, and others have antiplatelet activity and have demonstrated platelet-activating factor (PAF) receptor antagonist activity (17). Thus, ginkgo has been indicated to be a possible cause of postoperative bleeding (18, 19). Some case reports have suggested that patients taking drugs affecting platelet function and/or coagulation effects, such as warfarin or the NSAIDs aspirin (acetylsalicylic acid), ibuprofen or rofecoxib, experienced bleeding after self-prescribing ginkgo (1786 Izzo & Ernst[a] 2009) at recommended doses (20, 21, 22). Adverse events were especially severe for aspirin (reports of spontaneous hyphema) (23), warfarin (intracerebral haemorrhage (24) and ibuprofen (comatose state with an intracerebral mass bleeding of which the patient died) (21). Conversely, recent trials did not substantiate these outcomes. In one trial (25), ginkgo was found to potentiate the effect of cilostazol on bleeding time, however, no substantial association between bleeding time prolongation and platelet aggregation inhibition was determined. A systematic review of case reports established that ‘‘the causality between ginkgo intake and bleeding is

unlikely'' (26). The effect of ginkgo on CYP enzymes has been evaluated in clinical trials using, as probe drugs, alprazolam, midazolam, nifedipine (CYP3A4), caffeine (CYP1A2), chlorzoxazone (CYP2E1), debrisoquine (CYP2D6), tolbutamide, diclofenac, flurbiprofen (CYP2C9) and omeprazole (CYP2C19) (27, 28, 29, 30, 31, 32, 33, 34). Despite varying results, particularly for the CYP3A4 isoform, an effect on CYP enzymes by ginkgo seems questionable. The CYP2C19 isoform is a notable exception.

The idea that the combination of ginkgo and anticoagulant or antiplatelet drugs may correspond to a serious health risk is based on a number of case reports. Nonetheless, these findings were not substantiated by clinical trials. Ginkgo should be not taken concomitantly with CYP2C19 substrates, while the effect of ginkgo on CYP3A4 warrants further study.

4.3 Echinacea

Echinacea is a widely used herb, usually for the prevention and treatment of upper respiratory tract infections. It is formulated from plants belonging to the genus Echinacea, including E. purpurea, E. angustifolia and E. pallida (Fam Asteraceae). These varieties have phytochemical resemblances, but also noteworthy differences, particularly regarding the distinct alkylamides and their concentration, which are chemical constituents which are capable of modulating cytochrome P450 (CYP) activity. Used alone, echinacea is considered to be innocuous, with little risk for the consumer (35).

Reports regarding the effect of echinacea on CYP activity have shown conflicting results. Gorski et al. found that echinacea (E. purpurea roots), taken as1600 mg/day for 8 days, decreased the oral clearance of CYP1A2 substrates (but not the oral clearance of CYP2C9 and CYP2D6 substrates), as well as caused selective modulation of the catalytic activity of CYP3A4 at hepatic and intestinal sites in healthy volunteers (36). However, two other trials found no effect of echinacea on CYP1A2, CYP2D6, CYP2E1 or CYP3A4 (37, 38).

4.4. Garlic

Aside from culinary uses, garlic (Allium sativum L., Fam Liliaceae) is used as a medicinal herb for the treatment of hypercholesterolemia and the prevention of atherosclerosis. It has been suggested that garlic may exhibit an effect on platelet function and coagulation properties, which could lead to an increased risk of bleeding (39). In two patients previously stabilized on warfarin, the international normalized ratio (INR) changed after garlic intake according to one publication (40). However, two trials stated that garlic (enteric-coated tablets or aged garlic extract) made no alterations to the pharmacokinetics or pharmacodynamics of warfarin, and that garlic presents no serious hemorrhagic risk in sufficiently monitored patients on warfarin therapy (41, 42). Two clinical trials suggested that garlic oil may selectively inhibit CYP2El, as demonstrated by the decreased 6-hydroxychlorzoxazone/chlorzoxazone serum ratios, although not other CYP isoforms (such as CYPlA2, CYP3A4 or CYP2D6) (27, 28). Garlic powder demonstrated no effect on CYP3A4 (43, 44). Garlic may cause interactions in patients on antiretroviral therapy (39). A substantial decrease in the plasma concentrations of saquinavir, a protease inhibitor, was seen in healthy volunteers after taking garlic for 3 weeks (45). Acute dosing of garlic over 4 days did not considerably modify the single-dose pharmacokinetics of the protease inhibitor ritonavir (a CYP3A4 and P-glycoprotein substrate) (46). The reason for these incongruities is presently unclear.

Lastly, a clinical trial indicated that chewed raw garlic meaningfully reduced cholesterol and triglyceride levels, but did not significantly reduce serum cyclosporine levels in renal transplant recipients (47). Caution is recommended if garlic is taken along with CYP2El substrates or with antiretroviral drugs such as ritonavir and saquinavir. The likelihood of garlic causing over anticoagulation if administered concomitantly with anticoagulant drugs has not been established by clinical trials (41, 42).

4.5 Kava kava

Kava is a frequently encountered herb used to treat anxiety. Despite approximately 80 reported cases of possible hepatotoxicity, kava (Piper methysticum roots and rhizome) is enduringly popular (48). Clinical studies have demonstrated that kava exhibits an inhibitory effect on CYP2EI, however it did not show the same effect on other CYP isoforms, such as CYP3A4, CYP2D6 or CYPIA2, or P-glycoprotein (38). Individual case reports have indicated interactions of kava with levodopa, the antiparkinsonian drug, with consequent reduced efficacy (49), as well as with the alprazolam, a benzodiazepine, causing a semi-comatose state (50). These findings might have a pharmacodynamic basis, as kava is an antagonist of dopamine effects, which may elucidate the diminished efficacy of levodopa.

Kava may also interact with GABA receptors, much like with benzodiazepines (51). Therefore, kava should be not taken along with CYP2EI substrates, nor should it be taken with dopaminergic drugs or benzodiazepines.

5. Hypothesis

Based on a recent resurgence of popularity of ″natural medicine″ and ″alternative medicine″, we hypothesize that the trends of interest in herb-drug interactions over time will increase. We also hypothesize that herbal remedies will show an upward trend in internet-based search.

6. Objectives

The objective of this study is to determine the clinical relevance of common interactions of drugs and herbal supplements used in alternative medicine through public interest and knowledge of such interactions.

7. Material and Methods

The most frequently used herbs were used as keywords in the search criteria. We decided to incorporate Google Trends in our study to gain insight into patient behavior. Google Trends is an internet-based tool used to statistically analyze search data. Google Trends provides access to Internet search patterns by analyzing a portion of all web queries on the Google Search website and other affiliated Google sites (52). A description of the user interface is shown in Figure S1. Users can download the output of their searches to conduct further analyses. The portal determines the proportion of searches for a user-specified term among all searches performed on Google Search. It then provides a relative search volume (RSV), which is the query share of a particular term for a given location and time period, normalized by the highest query share of that term over the time-series (53, 54).

The data we sought to analyze was patient interest in supplements, supplement-drug interactions, and how public interest in these has changed over time. We also used Google Trends to compare public interest in specific search key words and phrases.

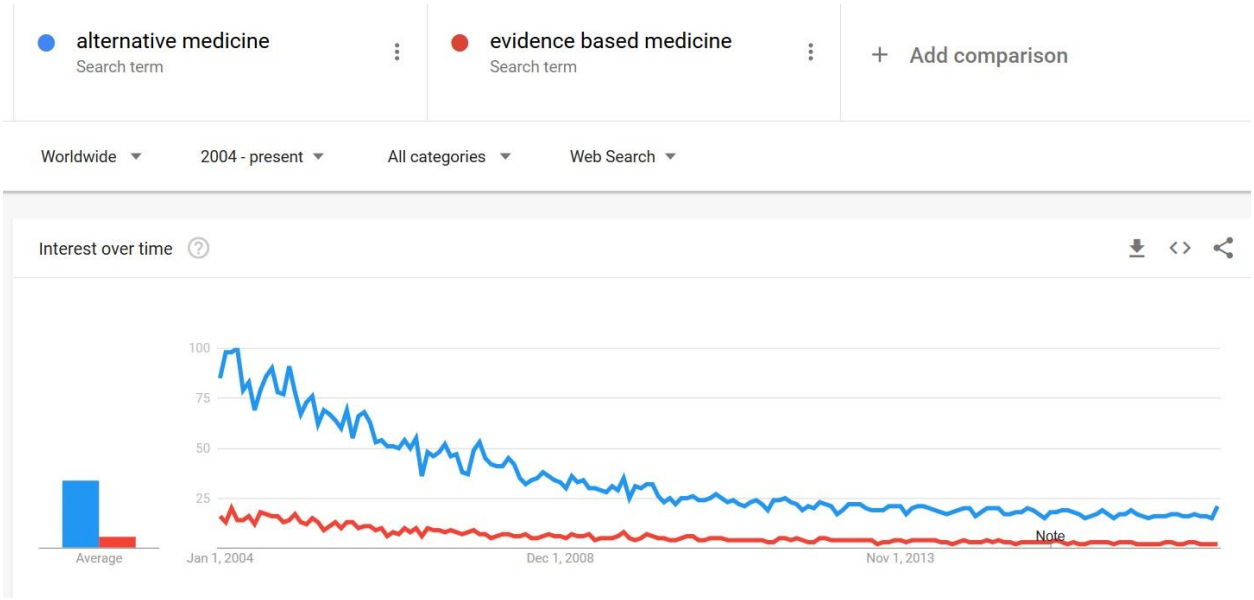
However, there is limited information on possible ways to utilize it, as well as its limitations. Filters applied to the search were ″worldwide″, ″2004-present″, ″all categories″, and ″web search″. The keywords and search terms used were ″herb–drug interaction″, ″st. john's wort″, ″st. john's wort interactions″, ″garlic interactions″, ″gingko interactions″, ″herbal remedies″, and ″herb – treatment interaction″.

Comparisons between ″alternative medicine″ and ″evidence-based medicine″ on Google Trends and follow up searches were done on Google for news articles. The search term used was ″death herbal drug″. The results included a recommendation that claimed people also searched for ″deaths due to herbal supplements″. This term was searched to see if there were any major news stories between 2004 and the present. An article titled ″Herbal medicines can be deadly, pathologist warns″ was found on Science Daily (55). The article reported a study emphasizing the potential dangers of herbal supplements including examples of such complications.

8. Results

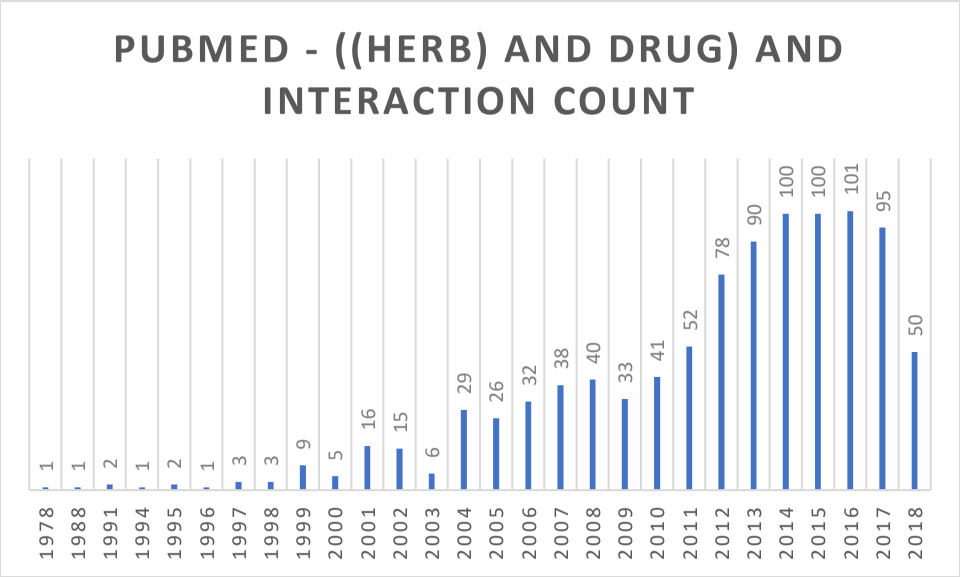
Despite herbal remedies being consistently searched as a term on the Google Trends search engine over time, we were surprised to find that the term ″herb-drug interaction″ produced no results. Likewise, no results appeared for the search terms: ″St. John's wort-drug interactions″, ″st. john's wort″, ″st. john's wort interactions″, ″garlic interactions″, ″gingko interactions″, or ″herb – treatment interaction″. ″herbal remedies″ showed a persistent decline from 2004-present.

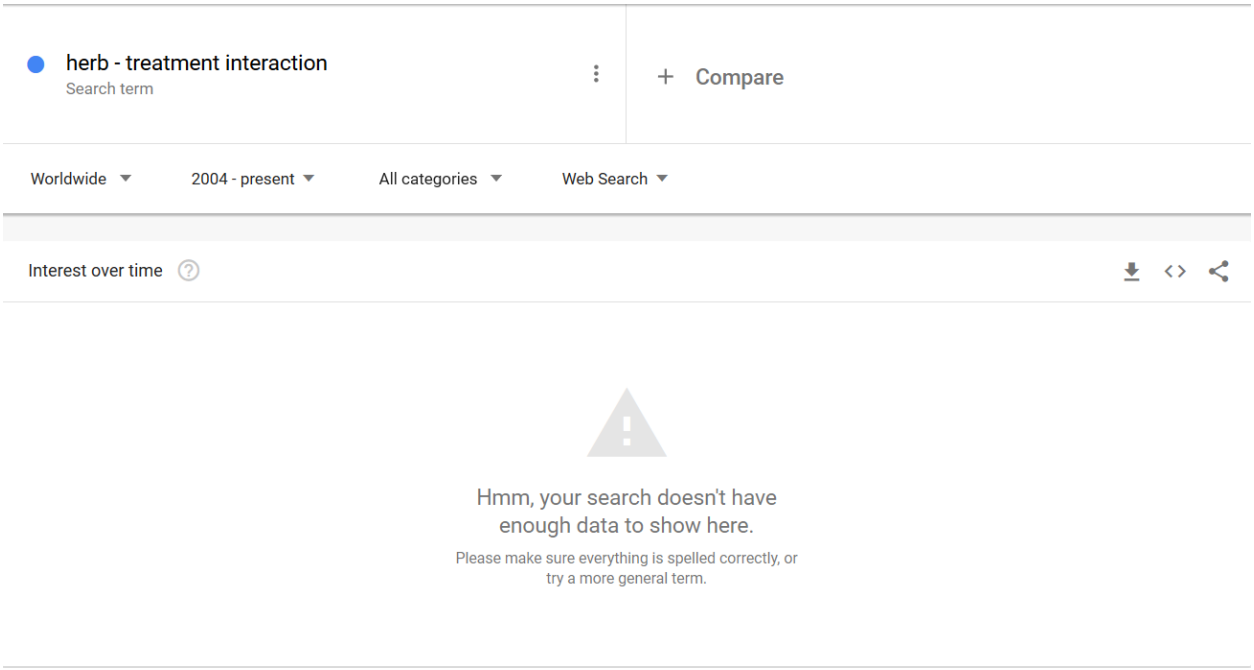
The comparison of ″st. john's wort interactions″ vs. ″warfarin interactions″ showed zero results for St. John's wort interactions, compared to warfarin, which showed consistent searches with steady variability.



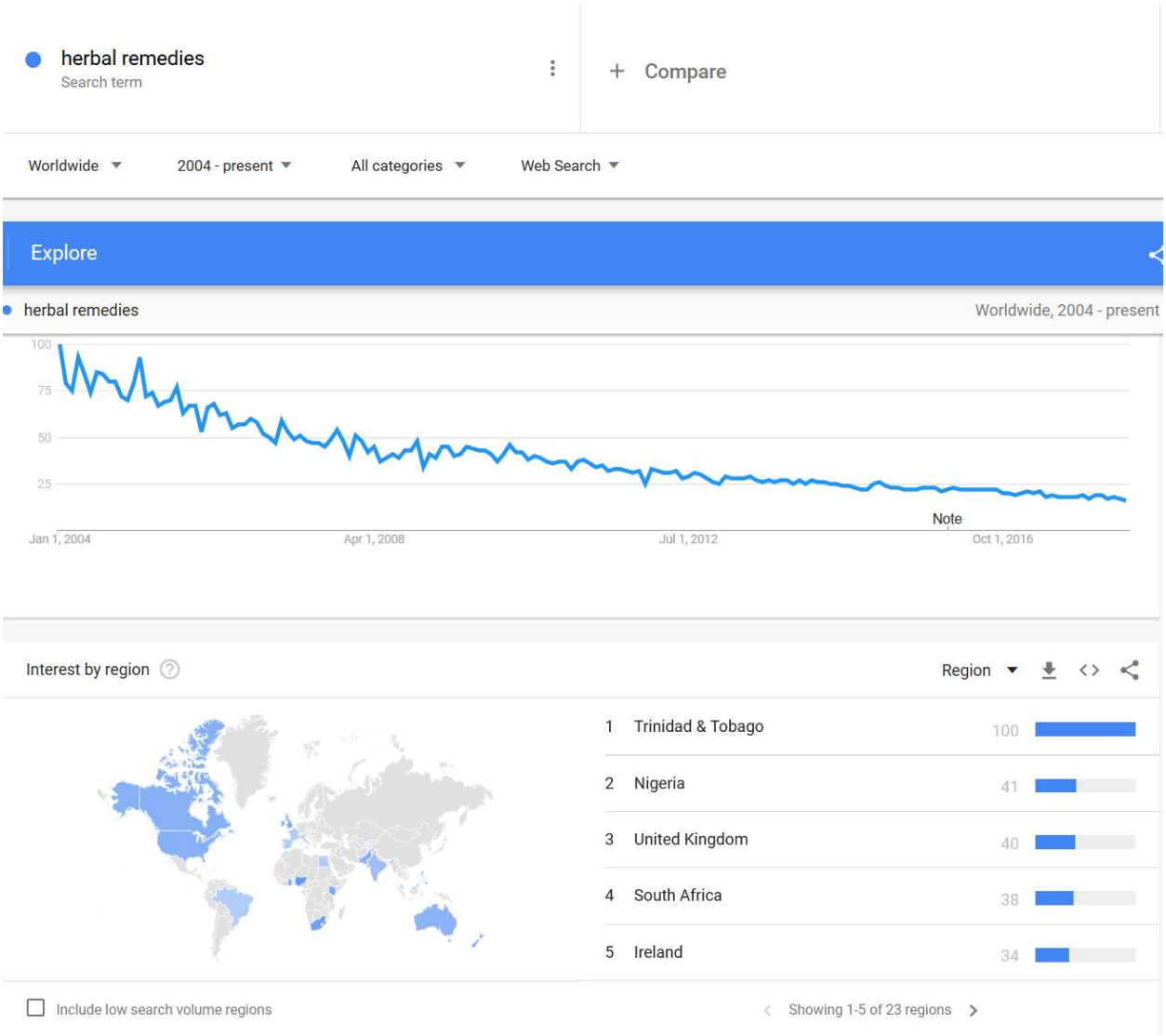
Screenshot 1. Google Trends ″alternative medicine″ vs. ″evidence based medicine″

Table 1. Pubmed search of ″herb+drug+interaction″

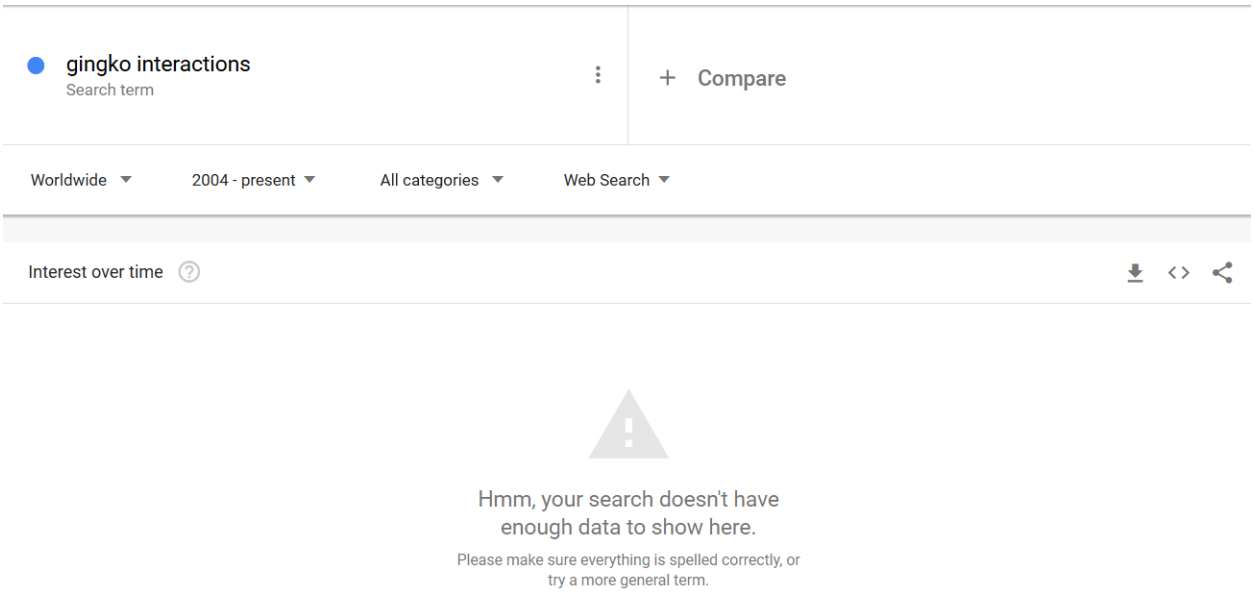




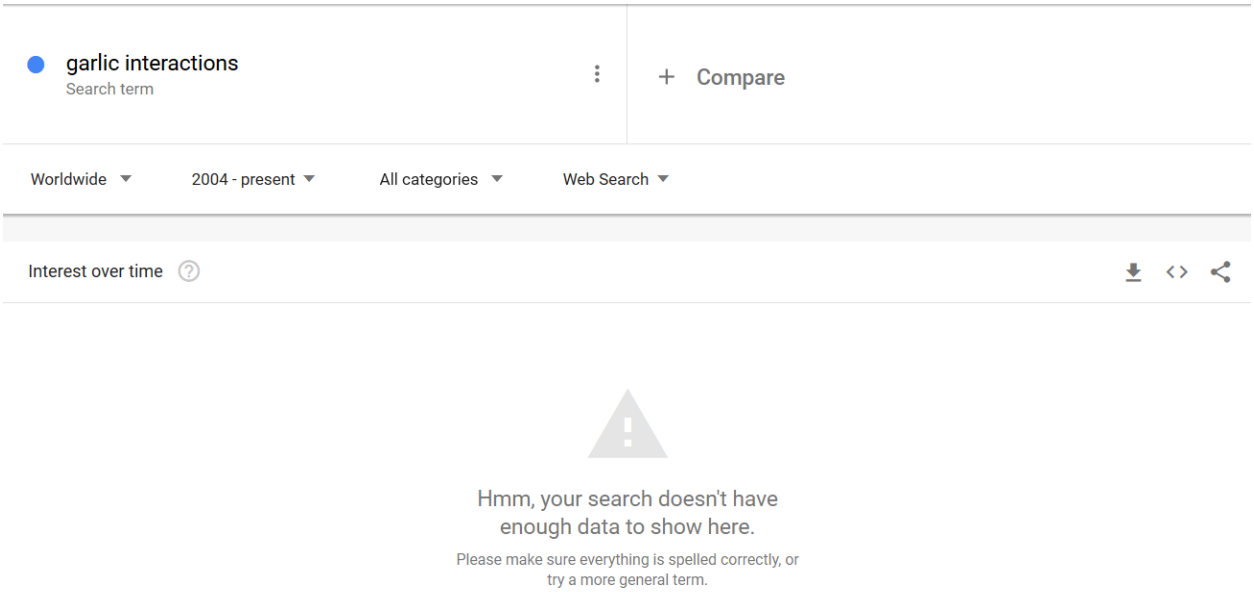
Screenshot 2. Google Trends ″herb – treatment interaction″



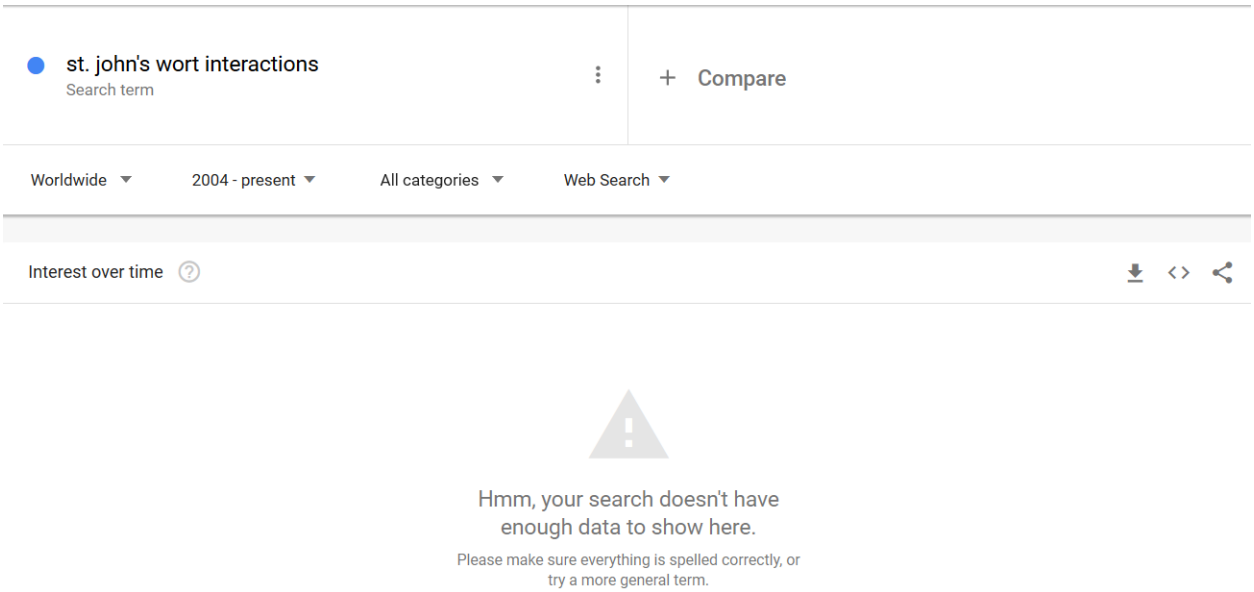
Screenshot 3. Google Trends ″herbal remedies″



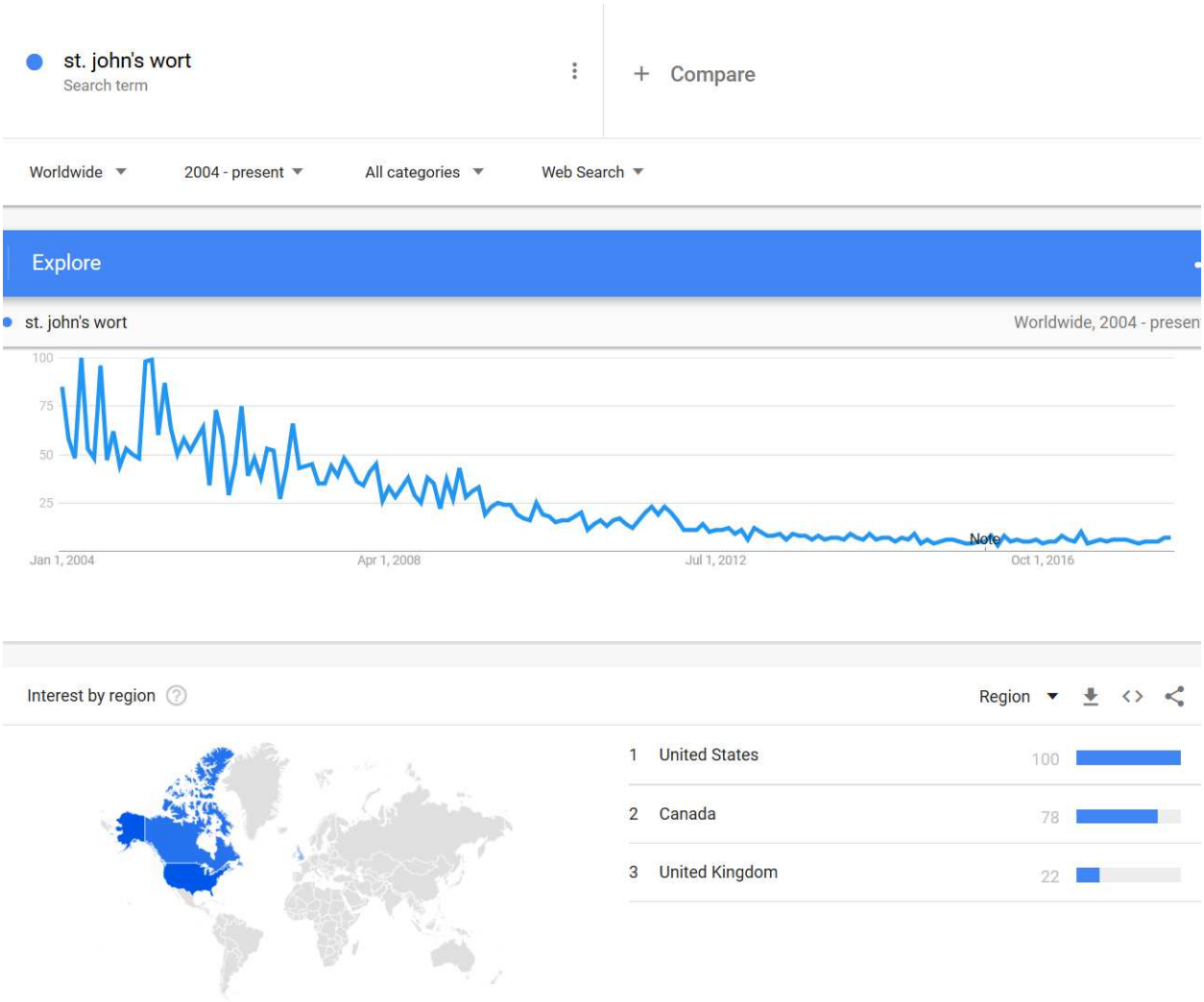
Screenshot 4. Google Trends ″gingko interactions″



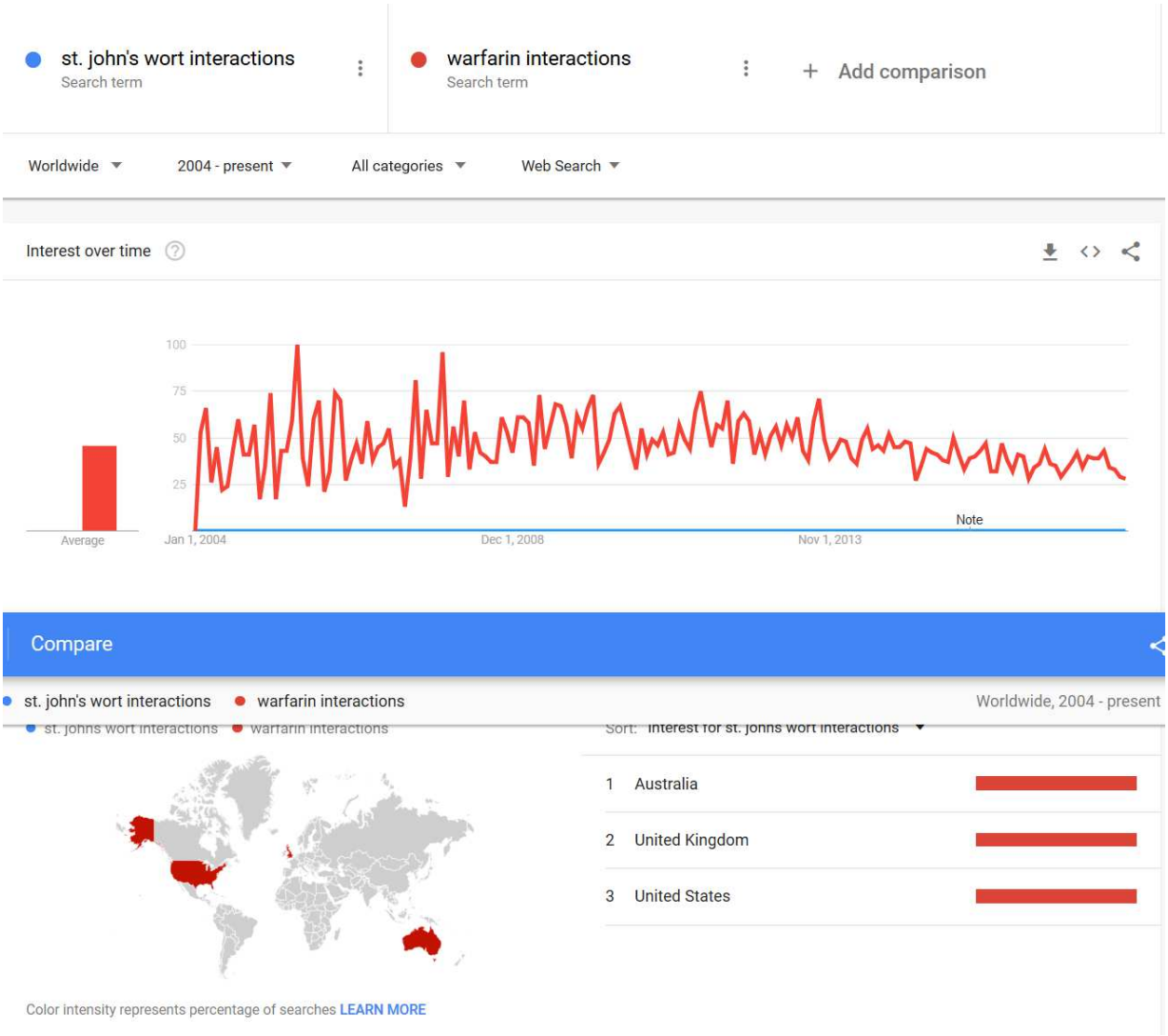
Screenshot 5. Google Trends ″garlic interactions″



Screenshot 6. Google Trends ″st. john’s wort interactions″



Screenshot 7. Google Trends ″st. john's wort″



Screenshot 8. Google Trends ″st. john's wort interactions″ vs. ″warfarin interactions″

9. Discussion

The data obtained was worrisome. In fact, we were astounded by the results. Obviously, Google Trends is a novel data collection tool and there is clearly a degree of error in the available data.

It is also important to note that there are limitations in the methodology used. Many different terms were applied to Google Trends to determine if there was any correlation between news articles regarding complications stemming from herbal supplement use. Even though none of these terms or phrases showed correlations between news stories and subsequent searches, that does not definitely rule out that such searches had not taken place. Specific terms/phrases might exist that do indeed show a correlation between adverse events in the news and searches on the internet.

The supposed lack of self-education of the general public on the use of herbal supplements emphasizes how important it is for the medical community to step in. An estimated 30% of US citizens use herbal supplements, often without their doctor's knowledge (55). This indicates that the medical community should be proactive in discussing the use of herbal supplements with patients. Herbal supplements have a reputation of being safe because they are ″natural″, but because there is virtually no regulation of their development, it is possible they can be anything but safe.

The Science Daily article referencing the dangers of herbal supplements was published in February of 2010. It is clear it's publication had little effect on increasing search terms referencing the dangers of herbal medicine as there is no appreciable changes seen in Google Trends in February 2010. In fact, when the phrase ″death due to herbal supplements″ was put into Google Trends, there was no data to be shown. This was concerning, as the term was recommended by Google as a phrase searched for in the past.

Educating patients on the topic should be done carefully so as not to alienate or upset them. Some patients might feel their autonomy is being threatened if they are criticized for using herbal supplements or feel the doctor has ulterior motives if they recommend terminating the use of a supplement.

It is important to point out that there is not only an increasing level of trust in herbal medicine but there is a concomitant decrease of trust in western medicine. A major factor that is

allowing the disbalance to occur simultaneously is the use of social media. Social media has the power to allow anecdotal stories to be used as proof that alternative therapies that are less harmful exist.

The British Academy of Royal Sciences conducted a survey in 2017 that showed only 37 percent of Britons believed evidence from medical research (56). Furthermore, roughly two thirds of those respondents felt family and friends are the most reliable sources for medical advice. The direct effect of this lack of trust can be correlated to the lack of knowledge of interactions between herbal therapies and western medicine.

A focus on evidence-based knowledge of certain supplements exists and that information should be shared neutrally. Also, any quality-control studies on specific products should be researched by the doctors and shared with the patients so at least they will know to avoid those particular brands.

10. Conclusions

The results of our analysis suggest that the popularity and on-line public search for knowledge of interactions between drugs and herbal supplements used in alternative medicine is indicative of the insidious, seemingly benign nature of herbal remedies used concurrently with prescription drugs. It is obvious that patients view herbal supplements as harmless additions to their health regimen, as evidenced by a lack of interest into potential harmful effects or interactions.

Google Trends is an undoubtedly useful tool in the analysis of commonly searched (or uncommonly searched) data. We believe there is much improvement to made in regard to the reliability of available data analysis, and look forward to seeing them implemented.

Regarding the use of herbal supplements, manufacturing companies must be held responsible to determine what possible interactions their products might be involved in and present clear statements regarding their results. It is essential to provide regulation to better control what herbal supplements contain and their exact composition. Furthermore, an interaction reporting domain must be put into place in order to facilitate reporting of instances of interactions.

We recommend that popular search engines (i.e. Google) should display a warning message about potential drug interactions when searching for alternative medicine compounds.

Care must be taken by physicians to inquire of their patient's herbal supplement usage, as well as discuss herbal supplements with patients. Furthermore, physicians should familiarize themselves with common herb-drug interactions so as to better provide information to their patients. This should be devoid of judgement, as the data shown here ascertains that patients will demonstrate interest in supplements regardless of whether or not they choose to disclose this information with their physician.

There is a need for more formal, human-subject studies to gain better knowledge of the prevalence of specific herb-drug interactions.

11. Acknowledgements

I would like to thank my Mentor, prof. Robert Likić, for his support and unwavering enthusiasm throughout my medical education, as well as in the making of this thesis.

I would also like to thank my future husband Dr. Tomislav Hrvoje Jagatić, for his insights and limitless expressions of support and encouragement, and for never ceasing to challenge me intellectually, as well as his patience with my outlandish formatting demands.

All of this would not be possible without the support and encouragement of my parents, Miro and Biserka Sanković. Thank you for standing behind me throughout these long years of my education.

Thank you for teaching me the value of hard work, determination, and the importance of staying true to yourself.

Thank you for believing in me when all seemed lost and north was a difficult direction to determine.

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13. Biography

Daniella Eva Sanković was born on January 19th, 1989 in Euclid, Ohio, USA. She moved to Croatia with her parents in 1998.

She completed the International Baccalaureate, and was accepted to the University of Zagreb School of Medicine English Program.

She worked as a Student Demonstrator for the subject of History Taking and Physical Examination, as well as a language editor on multiple scientific publications. She is a member of the Student Surgical and Cardiology Societies, as well as CroMSIC, StEPP (Student Emergency Medicine Program).

Concurrently with school, she worked as an English language teacher in conversational and children's English classes.

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