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ORIGINAL PAPERS

Meta-Analysis on some Plant Extracts Benefits on Neuropsychiatric Disorders Models Studied in Zebrafish

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Abstract. Background. Nowadays' society becomes increasingly interested in plant-based alternatives in order to treat various diseases. Humans worldwide are diagnosed with neuropsychiatric disorders like epilepsy, autism, Alzheimer's disease, Parkinson's disease, or ADHD (attention deficit hyperactivity disorder) and, consequently, research has been done in order to analyse different plant extracts' effects in their treatment, considering the various side effects conventional drugs could have. Judging by the neuroanatomical similarities to the human body and due to the advantages it has as experimental purpose animal, zebrafish (*Danio rerio*) has been preferred throughout the past years in the detriment of mammalian animal models. **Objectives.** This study aims to analyse the specialized literature regarding the benefits of phytotherapy in neuropsychiatric disorders treatment, using the zebrafish as animal model. **Methods.** This systematic analysis involved search engines like PubMed, Zfin, Semantic Scholar, Microsoft Academic, Scite and BASE (Bielefeld Academic Search Engine). Publications from 1960-2021 were used only, and reviews, conference articles or video/audio information were not selected in order to avoid redundancy, while journal articles were preferred. Different key words combinations were used to collect the articles related to the subject of interest. **Results.** Analysing the collected data, it can be concluded that zebrafish is increasingly used in behavioural, toxicological, or genetical research as descriptive or experimental model. Also, there is an expanding interest in using this species to investigate phytotherapy's benefits in neuropsychiatric disorders treatment.

Keywords: *phytotherapy, neuropsychiatry, zebrafish, plant extracts*

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Introduction

As continuous sources of biologically active compounds, plants became extremely important for the Animal Kingdom, both for nutritional and therapeutic purposes. Statistics show that there is an increasing interest in plants regarding their aromatic and medicinal compounds, as people become better informed about the benefits of phytotherapy.

Judging by the fact that an increasing number of people are nowadays trying plant-based treatments for various health issues, researchers focused on studying the effects some plants could have on a neurological level, by using the zebrafish as animal model due to its advantages as experimental purposes animal.

According to the DSM manual (Diagnostic and statistical manual of mental disorders), a psychiatric disorder is a syndrome characterised by cognitive function disruption or different behavioural changes that indicate psychological, biological, or development dysfunction. Seizures, attention or cognitive deficit disorders, paralysis, uncontrolled anger, eating disorders, anxiety or depression are just few examples of frequently diagnosed neuropsychiatric disorders (Stein *et al*, 2010).

Regarding the possible causes of mental disorders, studies claim that they are generated by cranial traumatisms, infections, as drug side effects or due to genetical factors, and the treatment varies depending on the cause - psychotherapy or medical treatment (Johnstone & Lawrie, 2016).

Schizophrenia, Alzheimer's disease, Parkinson's disease, epilepsy, and ADHD (attention deficit hyperactivity disorder) are few central nervous system pathologies that globally affect humans nowadays. Schizophrenia is represented by a series of hallucinations, usually triggered by acoustic stimuli as voices or noises, and patients have thinking, talking and social issues, uncapable of decision making (Dominguez *et al*, 2013). The Alzheimer's disease is a neurodegenerative disorder with unknown aetiology, where first symptoms observed at people younger than 65-70 years old are correlated with dementia-like family history (Nabavi *et al*, 2016).

Parkinson's disease is known for the complex way it affects the human brain, negatively impacting the dopaminergic and non-dopaminergic mechanisms (Jankovic, 2008). It is characterised by symptoms as shaking, muscular rigidity and posture instability, all these being signs of extended neurological injuries (Ball *et al*, 2019). Epilepsy is represented by episodical abnormal electric activity in some brain cells, negatively affecting the normal cognitive processes (Motamedi *et al*, 2003).

This study aims to make a systematic literature analysis regarding the benefits of phytotherapy in neuropsychiatric disorders treatment, using the zebrafish as animal model.

Zebrafish as animal model

Zebrafish – *Danio rerio*, is known as one of the most frequently used experimental purposes animals due to it has a series of advantages that recommends it as an ideal animal model: completely sequenced genome, facile genetic manipulation, high fertilization rate, quick embryo development (embryos develop complete organ systems 48 hours after fertilization) (Teame *et al*, 2019).

Facilitating the neurological development studies, zebrafishes have short reproductive cycles, transparent embryos, small sized larvae, and evolution patterns similar to humans' (Zon & Peterson, 2005). They can live in only 200 µl fluids, while there is an extremely low amount (a few mg) of chemical compound needed in order to study its effects (Best & Alderton, 2008).

Over the past years, zebrafishes have been used for numerous types of research subjects. For example, thanks to the quick embryo development, there was the possibility to examine in real time some vaccines' effects on important tissues and organs (Bailone *et al*, 2020). Similarly, they were helpful in different bacterial infections studies (Henry & Wlodkowic, 2019). Also, they were an important resource when studying the biology of telomeres during aging, regeneration, and in cancer related processes (Cavuela *et al*, 2019), considering the fact that zebrafishes could spontaneously develop tumors when they are 1 or 2 years old (Raby *et al*, 2020). Obesity, intestinal diseases and other frequently diagnosed human diseases have been analysed *on Danio rerio* individuals due to their anatomical and pshysiological similarities to the human body (Teame *et al*, 2019).

There is scientific proof suggesting that *Danio rerio* is an extremely useful animal model to study neurological disorders such as communication disorders, the autism spectrum disorder, or attention deficit hyperactivity disorder (ADHD) (Stein *et al*, 2010).

Neuropsychiatric disorders studied on zebrafish

Zebrafishes have successfully been used to establish the neurological and behavioural processes behind neuropsychiatric pathologies like epilepsy, Alzheimer's disease, Parkinson's disease, or schizophrenia (Paquet *et al*, 2010).

Frequently diagnosed in children and elders, **epilepsy** is a wide spectrum aetiology neurological disorder (Gawel *et al*, 2019). Characterised by abnormal electrical activity in the brain, this pathology contributes to irreversible brain damage that could further lead to death. Conventional recommended drugs' mechanism of action implies reduction or prevention of sodium currents or positive modulation of the gamma-aminobutyric acid (GABA). However, 1 out of 3 patients develops drug-resistance, fact that encourages more biomedical research and improvements to be done (Fontana *et al*, 2018). Genetical homology of zebrafishes to humans made it easy for researchers to use them in epileptic

treatment studies. Also, they meet all the criteria involved in epilepsy research on animal models: facile video behaviour analysis, electroencephalograms both for larvae and for adults, and brain imaging using bioluminescence.

A large number of *in vitro* and *in vivo* studies proved that many factors such as low levels of acetylcholine, oxidative stress and beta-amyloids build-ups could be involved in **Alzheimer's disease** pathophysiology. In order to analyse a possible drug for treating this pathology, zebrafishes have been used in research in the detriment of rodents, due to their economic advantages (Huang *et al*, 2016) and thanks to the neuroanatomical similarities shared with humans (Saleem & Kannan, 2018).

Parkinson's disease develops naturally in animals and could take even decades till symptoms are visible in humans. Zebrafishes are preferred as animal models in Parkinson's disease studies as their transparent embryos and larvae allow the usage of non-invasive imagistic methods to investigate the neural integrity, proteostasis (protein homeostasis), mitochondrial functions or microglial cells' activity at transgenic individuals (Barnhill *et al*, 2020). Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to cause loss of dopaminergic neurons and, consequently, causing Parkinson's disease in humans. As a matter of fact, fishes were exposed to it in order to analyse its effects on every embryologic development stage (Vaz *et al*, 2018).

Zebrafishes have been helpful in **autism** studies as well, especially by being animal models in genetical risk factors analysis. Considering the high heredity in autism, various zebrafish studies have been made to investigate the genetics behind this neuropathology. For example, human autism related 16p11.2 chromosomal region has a homologous region in zebrafishes (few genes important in brain development), fact that made it possible to conclude that it is involved in autism pathogenesis in humans as well (Stewart *et al,* 2014).

ADHD's phenotypes – attention deficit, impulsivity, and hyperactivity have all been described using different zebrafishes video monitored analyses. Similar to rodents, ADHD zebrafishes have modified dopamine levels, leading to hyperactivity and lack of attention (Fontana *et al*, 2018).

Phytotherapy in neuropsychiatric disorders

According to the World Health Organisation (WHO), phytotherapy is plant-based medicine, represented by products that contain plants' active compounds. Plant-derived drugs are 25% from the entire USA drug market.

Phytotherapy as epileptic treatment. As nowadays' epileptic treatment is considered inefficient because of its side effects, many studies on plant-based medication have been done (Gurria *et al,* 2020). Various plant extracts were reported as having efficacity comparable with synthetic drugs'. For example, *Aegle marmelos* has acetylcholinesterase inhibitory activity, *Acorus calamus* reduces seizures induced by MPTP and also has neuroprotective effects.

Phyllanthus longiflorus and *Centranthus longiflorus* cause sedation effects similar to diazepam's (Sucher & Carles, 2015), while *Plantago major* has been used in epileptic treatment both alone and in combination with other species, being known for pain release (Najafian *et al*, 2018).

Phytotherapy in Alzheimer's disease treatment. One of the plants used in Alzheimer's disease treatment is *Petroselinum crispum*, containing essential oils like myristicin, limonene, eugenol, and alpha-thujene, important in neurological degeneration prevention. *Thymus vulgaris* essential oils involves phenols like thymols, carvacrol, cinnamon, and pinene, that could have inhibitory activity on acetylcholinesterase and, therefore, prevent Alzheimer's disease. Garlic, *Hypericum perforatum*, and rosemary are also known for their neuroprotective actions (Nabavi *et al*, 2016).

Phytotherapy in dementia treatment. Nowadays, the best dementia treatment involves a series of drugs meant to inhibit acetylcholinesterase activity, but plant-based drugs could also improve dementia symptoms. Studies proved that *Salvia officinalis, Melissa officinalis,* curcumin and alcaloids like caffeine could prevent the cognitive function decrease and improve neuropsychiatric symptoms (Ghorani-Azam *et al,* 2018). Curcumin administration is more effective than placebo in depressive symptoms reduction and the best results were observed in middle-aged patients who followed the treatment for long periods of time (Lopresti, 2017).

Phytotherapy for zebrafishes' neuropsychiatric disorders treatment. Using zebrafishes for potential drug discoveries was proposed 58 years ago (Crawford *et al*, 2008). Nowadays, they are involved in various studies, helping researchers investigate different pharmacological processes, due to their high fertilization rate and transparent organogenesis (Dos Santos *et al,* 2016).

A 2012 study (Zhang, 2012) used zebrafishes to evaluate ethanol's neuroprotective effect from *Alpinia oxyphylla*. The results showed that this extract could prevent and repair the neurodegeneration induced by 6-OHDA (6-hydroxydopamine) and also improve locomotor activity in Parkinson's disease (Dos Santos, 2016).

Cannabidiol (CBD), present in *Cannabis sativa*, is proved to have strong antineoplastic activity. Also, *Magnolia officinalis* extracts like magnolol and honokiol have strong inhibitory effects on locomotor and brain hyperactivity in zebrafishes larvae (Li *et al,* 2020).

Berberine (Zhang *et al,* 2020) and linarin are frequently used in anti-Alzheimer treatment as they improve behavioural deficiencies in zebrafishes by inhibiting acetylcholinesterase activity.

Plants like *Aloysia polystachya* are often used in treating anxiety and depression. Some studies proved that even *Coriandrum sativum* generates sedative and anxiolytic effects (Zenki *et al*, 2020).

Cyperus articulates is traditionally used in Camerun to treat epilepsy. Its dried rhizomes contain many high polarity solvents and, consequently all these extracts were studied regarding their antiseizure activity using zebrafishes that were initially treated with pentylenetetrazol (PTZ) in order to induce the specific symptoms. Results showed that hexane extract from *C. articulates* reduced the PTZ induced seizures by 93% (Brillatz *et al*, 2019).

Table 1. Plant species and their beneficial effects in treating neuropsychiatric disorders

Plant species	**Family**	**Benefits**	**Reference**
Curcuma longa	*Zingiberaceae*	Alzheimer's disease prevention	Alafiatayo *et al*, 2019
Solanum torvum	*Solanaceae*	Antiseizure	Muniandy, 2018
Salviae miltiorrhizae	*Lamiaceae*	Antioxidant properties	Dos Santos *et al*, 2016
Magnolia officinalis	*Magnoliaceae*	Anxiolytic, antiinflammatory, antitumor, antiepileptic	Li *et al*, 2020
Cannabis sativa	*Cannabaceae*	Antineoplastic	Li *et al*, 2020
Anemarrhena asphodeloides	*Asparagaceae*	Brain injury treatment	Li *et al*, 2020
Scutellaria baicalensis	*Lamiaceae*	Antiseizure & neuroprotective	Li *et al*, 2020
Cymbopogon citratus	*Poaceae*	Central nervous system and gastrointestinal diseases treatment	Hacke *et al*, 2020
Valeriana officinalis L	*Caprifoliaceae*	Anxiolytic effects	Hacke *et al*, 2020
Spondias mombin L	*Anacardiaceae*	Anxiolytic and antidepressant effects	Hacke *et al*, 2020
Piper sarmentosum	*Piperaceae*	Tissue regeneration	Abidin *et al*, 2020
Berberina	*Berberidaceae*	Neuroprotective & neurotrophic effects	Zhang *et al*, 2020
Chrysanthemum morifolium	*Asteraceae*	Acetylcholinesterase inhibitory activity	Wang *et al*, 2021
Rosemary	*Lamiaceae*	Neuroprotective	Wang *et al*, 2021
Eucommia ulmoides	*Eucommiaceae*	Parkinson's disease treatment	Wang *et al*, 2021
Aloysia polystachya	*Verbenaceae*	Anxiolytic and antidepressant effects	Costa de Melo *et a*l, 2019
Coriandrum sativum	*Apiaceae*	Anxiolytic and sedation effects	Zenki *et al*, 2020

-Passiflora coerulea, *-Matricaria recutita,* *-Valeriana officinalis,* *-Salvia guaranitica,* *-Tilia europeae* *-Tilia tormentosa*	*-Passifloraceae* *-Asteraceae* *-Caprifoliaceae* *-Lamiaceae* *-Malvaceae*		
Cyperus articulatus L	*Ciperaceae*	Epileptic treatment	Brillatz *et al*, 2020
Aspergillus insuetus	*Trichocomaceae*	Antiseizure	Copmans *et al*, 2019
Codonopsis pilosula *Codonopsis lanceolata* *Codonopsis radix*	*Campanulaceae*	Antitumor effects	Wang *et al*, 2020
Tapinanthus globiferus	*Loranthaceae*	Antiseizure	Dietrich, 2017
Alpinia oxyphylla	*Zingiberaceae*	Increases locomotor activity	Kanathip *et al*, 2021
Streblus asper	*Moraceae*	Dementia prevention	Kanathip *et al*, 2021
Ceratonia siliqua L	*Leguminosae*	Anti-neurodegeneration Increases locomotor activity	Abidar *et al*, 2020
Moringa oleifera sp	*Moringaceae*	Reduces stress	Khor *et al*, 2018
Hypericum perforatum	*Clusiaceae*	Antidepressant	Sarris & Kavanagh, 2009
Piper methysticum	*Piperaceae*	Anxiety treatment	Sarris & Kavanagh, 2009
Tephrosia purpurea	*Fabaceae*	Alzheimer's disease prevention	Pitchai *et al*, 2018

Methodology

In the first section of this study, we used public data available on international academic data bases. The systematic meta-analysis involved the following search engines: PubMed, ZFIN, Semantic Scholar, Microsoft Academic, Scite and BASE (Bielefeld Academic Search Engine). Publications from 1960-2021 were used only. In order to avoid redundancy, reviews, conference articles, video /audio information was avoided, and journal articles were preferred. Key words like zebrafish, danio rerio, psychiatry, neurology, schizophrenia, Parkinson, autism, Alzheimer, and epilepsy were used in different combinations to collect publications related to neuropsychiatric disorders in zebrafishes. The same key words were also connected to plant names (*Solanum torvum, Rehmannia, Rhynchosia, Dysoma, Pharbitis*) or bioactive compounds (alkaloid, glucoside, polyphenol, terpenes, berberine, caffeine, vincamine,

phytoestrogen) in order to collect data regarding the effect of different plant extracts in treating neuropsychiatric disorders induced in zebrafishes.

In order to find out the geographical distribution of the studies worldwide, key words like zebrafish/danio rerio and "country of interest" were used. Countries were sorted after authors affiliation to an institute or university.

Results and discussion

Table 2. Total number of articles found on specific search engines based on given key words

Search engine	Key word - zebrafish	Key word – danio rerio
Scite	40982	8157
Zfin	43548	8181
Semantic Scholar	39100	8370
Base	52384	9458
Microsoft Academic	44579	33370
PubMed	43545	43907

Total number of articles found using both key words – zebrafish and danio rerio on PubMed was 43534, due to the fact that, in most of the studies, authors used both of the key words in their terminology.

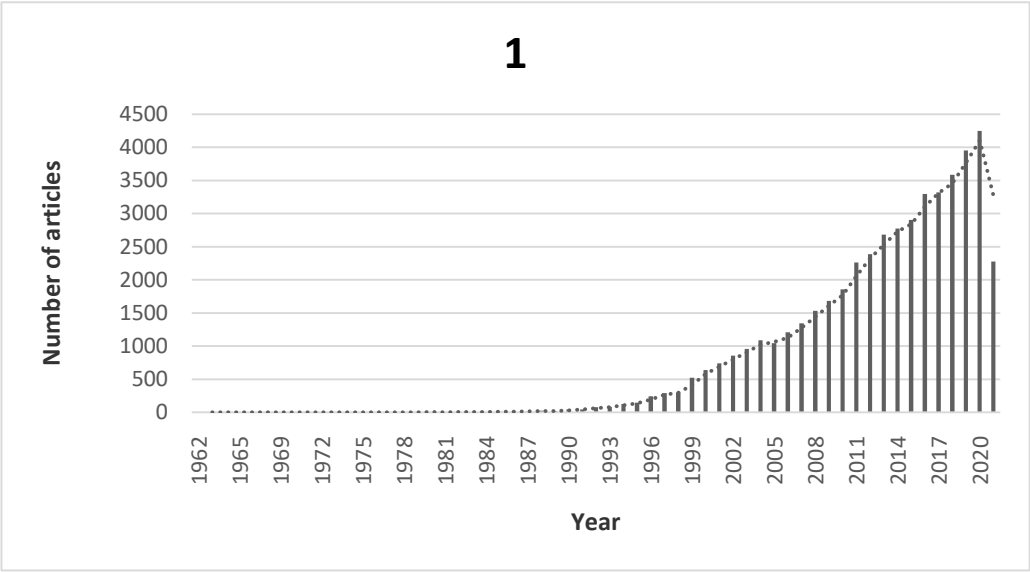

Figure 7. Increasing number of searches about Danio rerio over the past years

Based on the annual number of published articles, it was noticeable that over the last 20 years there was an increasing number of zebrafish studies. In 2000, there were 641 published articles, while in 2020 PubMed database had 4251

zebrafish related publication, fact that suggests increasing interest in using this species as animal model.

Number of phytotherapy related studies on zebrafishes found based on specific key words searches are: phytotherapy – 29, herbal medicine – 193, herbal – 234, extract – 1402, plant – 1513, alkaloid, glycoside, polyphenol, terpenes – 1862, berberine, caffeine, vincamine, phytoestrogen – 155, solanum torvum, rehmannia, rhynchosia, pharbitis, dysoma, ligusticum – 13. Considering the annual number of publications over the past 2 decades, it increased 5 times during years 2003-2005 regarding the articles related to phytotherapy, while during 2000-2020, it increased 25 times for plants related articles, 34 times for extracts related articles, and 16 times for alkaloids, glycosides, polyphenols, and terpenes.

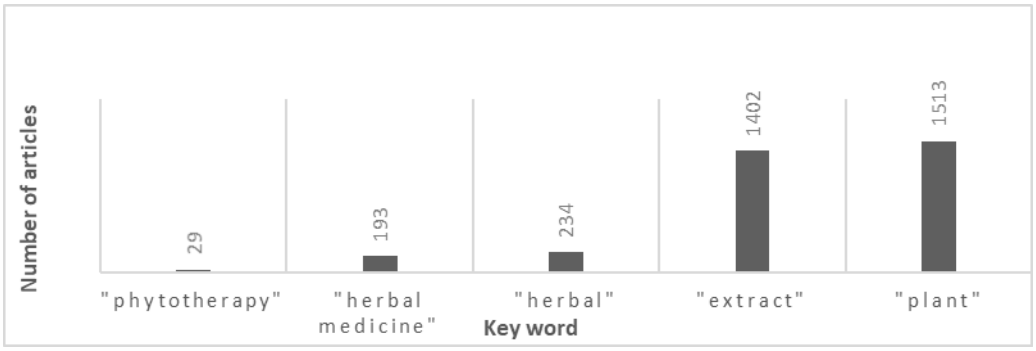

Figure 8. Total number of Danio rerio phytotherapy related articles

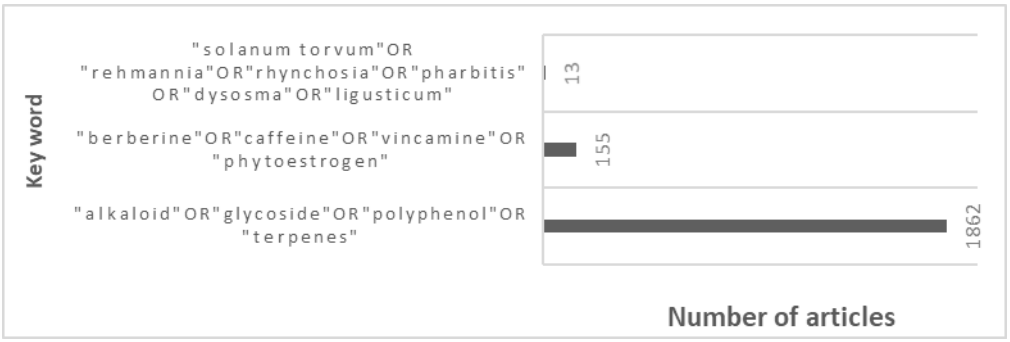

Figure 9. Total number of articles about phytochemicals' effects studied on Danio rerio

Considering the neuropsychiatric disorders studies made about zebrafish, we collected the following data:

Table 3. Total number of articles about neuropsychiatric disorders in Danio rerio

Key word	Number of articles found
ADHD	35
Schizophrenia	122
Autism	174
Parkinson	308
Alzheimer	331
Epilepsy	333
Psychiatry	386
Neurology	666

Danio rerio studies regarding the neuropsychiatric disorders also multiplied over the past 20 years. There was a 63 times rise of psychiatry related articles, 26 times more neurology articles, a 29 times rise for the number of articles about Parkinson's disease, 10 times for Alzheimer's, 24 for autism and 7 time more schizophrenia related articles. There were no changes in the number of articles about ADHD.

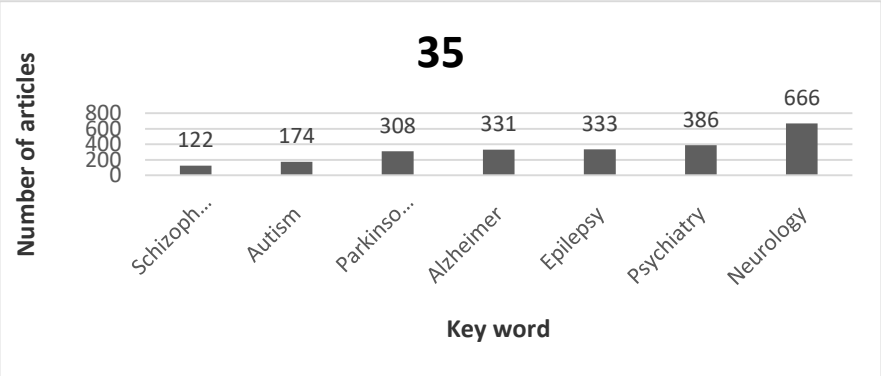

Figure 10. Total number of articles about neuropsychiatric disordes studied on zebrafish

Studies regarding the plant-based treatment of neuropsychiatric diseases in zebrafishes:

Table 4. Total number of articles about neuropsychiatric disorders
and phytotherapy based on different key words combinations

Key words	Number of articles
Phytotherapy + neuropsychiatric disorders	6
Herbal + neuropsychiatric disorders	9
Plant+ neuropsychiatric disorders	53
Extract + neuropsychiatric disorders	54

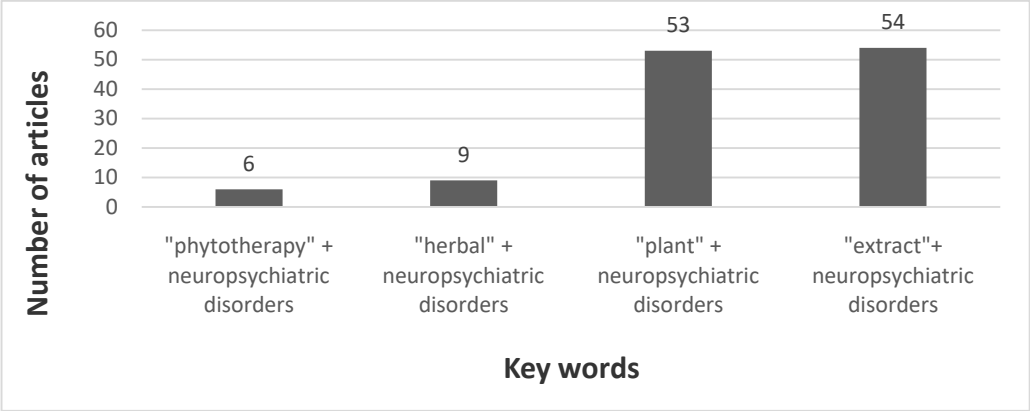

Figure 11. Total number of articles about neuropsychiatric disorders and phytotherapy based on different key words combinations

We found out that during 2010-2020 there was a decrease of number of articles searched by phytotherapy and neuropsychiatric disorders key words, while there was an increase for the other ones.

Regarding the most active countries in zebrafish research, the top 3 are: USA, China, and Germany. Countries with high research budget also have a high number of published articles.

Table 5. Total number of zebrafish studies according to the country the research was made

Country	**Number of published articles**
Israel	446
Sweden	692
Singapore	737
East Europe	622
Poland	220
Czech Republic	147
Hungary	123
Republic of Moldova	0
Bulgaria	8

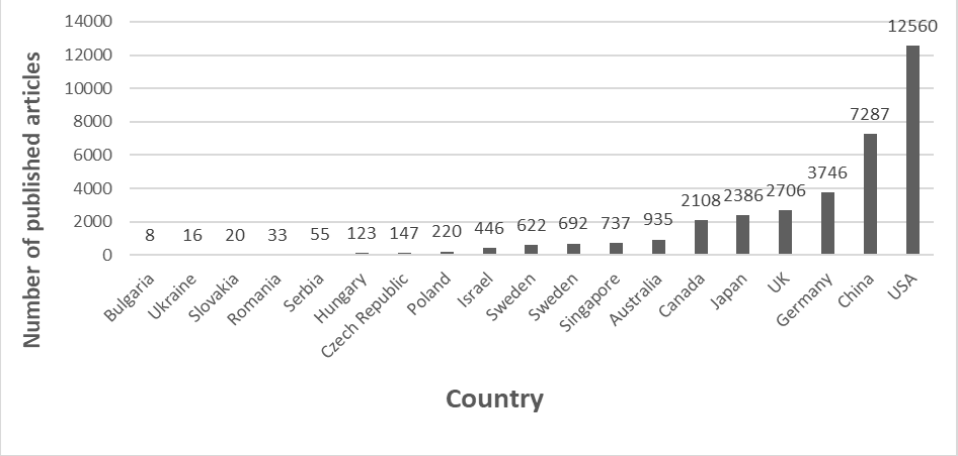

Figure 12. Total number of zebrafish studies according to the country the research was made

Conclusions

Analysing this study's results, it can be concluded that zebrafish (*Danio rerio*) is increasingly used in behavioural, genetical or toxicological research as descriptive or experimental animal model.

Nowadays, there is an expanding interest in using this species to analyse phytotherapy's effects in neuropsychiatric disorders treatment, while trying to reduce until the elimination the mammalian experimental animal model. Due to the high reproduction rate, low costs and small sized experimental place needed, the zebrafish animal model is the ideal alternative to experiments done on mammals.

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