Apiterapi ve Doğa Dergisi
Journal of Apitherapy and Nature
www.dergipark.gov.tr/jan

Rheumatoid Arthritis – Is There a Role for Apitherapy? Analysis of Books Written by Apitherapists Shows that Most Recommendations are Not Evidence-Based

Romatoid Artrit – Apiterapinin Rolü Var mı? Apiterapistler Tarafından Yazılmış Kitapların Analizi, Önerilerin Çoğunun Kanıta Dayalı Olmadığını Gösteriyor

Karsten MÜNSTEDT

Ortenau Clinic Offenburg-Kehl, Offenburg, Baden-Württemberg, Germany.

karsten.muenstedt@web.de, ORCID: 0000-0003-4273-5964

Received/Geliş Tarihi: 25/12/2021

Accepted/ Kabul Tarihi: 29/12/2022

***Corresponding author** /Yazışılan yazar

Doi: 10.35206/jan.1045529

e-ISSN: 2667-4734

Abstract

Apitherapy is a therapeutic approach based on the use of beehive products. It is frequently suggested for the treatment of rheumatoid arthritis. This study was to assess the recommendations of apitherapists regarding the treatment of rheumatoid arthritis. 129 books written by apitherapists were reviewed regarding their recommendations for rheumatoid arthritis. These recommendations were compared to the findings of preclinical and clinical studies on the subject. Sixty-eight (52.7%) of the books mention the topic of rheumatoid arthritis and there were 44 different recommendations. They include all bee products (honey, pollen, propolis, etc.) but mainly bee venom (15 times) and royal jelly (5 times). Bee venom acupuncture (apipuncture) is mentioned only once. Compared to analyses from the scientific literature, only bee venom but mainly apipuncture are supported. This analysis shows that the majority of apitherapeutic books do not provide adequate information. However, some reports supported the scientific evidence that bee venom and apipuncture could be an interesting means of treatment of rheumatoid arthritis but more and higher quality clinical investigations are necessary.

Keywords: Apitherapy, Bee venom, Honey, Propolis, Rheumatoid arthritis

Özet

Apiterapi, arı kovanı ürünlerinin kullanımına dayalı bir tedavi yaklaşımıdır. Romatoid artrit tedavisi için sıklıkla önerilmektedir. Bu çalışma, apiterapistlerin romatoid artrit tedavisine ilişkin önerilerini değerlendirmek amacıyla yapılmıştır. Apiterapistler tarafından yazılan 129

kitap, romatoid artrit önerileri açısından gözden geçirilmiştir. Bu öneriler, konuyla ilgili klinik öncesi ve klinik çalışmaların bulgularıyla karşılaştırılmıştır. Kitapların 68'i (%52.7) romatoid artrit konusuna değinmektedir ve 44 farklı öneri bulunmaktadır. Bu öneriler tüm arı ürünlerini (bal, polen, propolis vb.) içermekle birlikte başlıca arı zehiri (15 kez) ve arı sütüne (5 kez) değinilmiştir. Arı zehri akupunkturundan (apipunktur) sadece bir kez bahsedilmiştir. Bilimsel literatürdeki analizlerle karşılaştırıldığında, sadece arı zehri ancak ağırlıklı olarak apipunktur desteklenmektedir. Bu analiz, apiterapötik kitapların çoğunun yeterli bilgi sağlamadığını göstermektedir. Bazı araştırmalar arı zehri ve apipunkturun romatoid artrit tedavisine yönelik farklı bir tedavi yaklaşımı olabileceğine yönelik bilimsel kanıtları desteklemekte olup bununla birlikte bu konuda daha fazla ve daha kaliteli klinik araştırmalara ihiyaç vardır.

Anahtar Kelimeler: Apiterapi, Arı zehri, Bal, Propolis, Romatoid artrit

1. INTRODUCTION

Rheumatoid arthritis (RA) is defined as a usually chronic autoimmune disease that is characterized especially by pain, stiffness, inflammation, swelling, and sometimes destruction of joints. The chronic inflammation of the synovial membranes leads to the destruction of cartilage and the adjoining bone, with the destruction of affected joints. Typical symptoms include pain, restriction in mobility, and fatigue, as well as inflammations of tendon sheaths, blood vessels, and internal organs. According to the 2010 American College of Rheumatology/European League Against Rheumatism, the classification criteria for rheumatoid arthritis are based on a score based on four criteria (Aletaha et al., 2010):

- Joint involvement (number of joints involved, especially small joints)
- Serology (positivity of rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA)
- Acute-phase reactants (abnormal C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)
- Duration of symptoms (< 6 weeks or ≥ 6 weeks)

Rheumatoid arthritis is the most common chronic inflammatory joint disorder in industrial countries. Its prevalence varies between 0.5% to 1.0% in the adult population. Women are more frequently affected than men. A study in the UK found the minimum population prevalence of RA is 1.16% in women and 0.44% in men (Institute for Quality and Efficiency in Health Care, 2015; Littlejohn & Monrad, 2018).

Early diagnosis and initiation of treatment are of great importance. If rheumatoid arthritis is diagnosed and treated within 3 to 6 months after the onset of symptoms, the immunological process can be influenced significantly; otherwise, the course of the disease

may vary greatly (Institute for Quality and Efficiency in Health Care, 2015; Littlejohn & Monrad, 2018).

Because of the importance of the disease, treatment guidelines have been issued by various national societies, e.g. Deutsche Gesellschaft für Rheumatologie (German Rheumatology Association) (Fiehn et al., 2018). The main aspects of these guidelines include that:

- Patients with functional restrictions should receive physiotherapy in order to maintain physical fitness and for the short-term reduction in pain. These patients should receive occupational therapy.
- Methotrexate is considered to be the treatment of the first choice.
- Administration of glucocorticoids is suggested until initial therapy achieves an effect. Afterward, glucocorticoids should be reduced as rapidly as feasible.
- In more complicated cases (intolerance to methotrexate, high disease activity, failure to respond to tocilizumab) patients should receive TNF-α antagonists, tocilizumab, a monoclonal antibody against the interleukin-6 receptor or tofacitinib, a Janus kinase inhibitor or rituximab.
- For the treatment of pain and joint stiffness, the use of non-steroid anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX)-2 inhibitors are recommended.

Although there are many treatment options in conventional medicine, many patients consider and use methods from so-called integrative, complementary or alternative medicine (CAM). User rates and the dominant CAM methods vary greatly between countries. In India, only 26.2% of patients with rheumatoid arthritis used CAM, mainly Ayurveda (Bhalerao et al., 2013). Of the patients in Turkey, 46.9% used herbs taken orally, nutritional supplements, and mind-body therapies (Tokem et al., 2014), whereas in Korea 82% of the patients had used CAM, mainly traditional Oriental medical treatments, plant- and animal-derived over-the-counter healthcare products, and manual therapies (Lee et al., 2008).

A recent systematic review of randomized controlled trials identified and analyzed 60 good-quality trials using CAM as an intervention for patients with rheumatic diseases. In the main, acupuncture was considered effective in the many trials relating to acupuncture, ayurvedic treatment, homeopathic treatment, electricity, natural products, megavitamin therapies, chiropractic or osteopathic manipulation, and energy healing therapy (Phang et al.

2018). However, different authors consider far more therapies to be potentially beneficial (Fernández-Llanio et al., 2016): fasting followed by a vegetarian diet, Mediterranean diet, fish oil, virgin olive oil, vitamin D, probiotics, herbal medicinal products (*Tripterygium wilfordii*), physical activity, yoga and tai chi, meditation/mindlessness, acupuncture, homeopathy, and balneotherapy/hydrotherapy.

Today's literature largely ignores a very old type of treatment – apitherapy. It is defined as the use of substances produced by honeybees (such as venom, propolis, or honey) to treat various medical conditions. According to other publications, the use of bee venom for rheumatism or arthritis has a long history that can be traced back to ancient Egypt, Greece, and China (Chen et al., 2010). Today, apitherapy is widely promoted by apitherapeutic societies all over the world and beekeepers (https://apitherapy.com/addresses/societies/; accessed April 2nd, 2020). It must be noted that there are two different directions: scientific apitherapy and holistic apitherapy. Holistic apitherapy can be considered as a part of complementary and alternative medicine and is largely promoted in books, apitherapeutic congresses, and beekeeping congresses. However, personal experiences and treatment concepts of holistic apitherapists are mainly published as books being guidelines for other practitioners since there are no uniform concepts for the education of apitherapists.

So far, there have been no detailed reviews on the potential benefits of holistic apitherapy for rheumatoid arthritis. Therefore we

- analyzed the recommendations in various apitherapy books
- analyzed the scientific evidence of bee venom therapy
- tried to answer the question of whether apitherapy could be a reasonable means of treatment of rheumatoid arthritis for patients who wish to use methods from integrative, complementary, or alternative medicine.

2. MATERIALS and METHODS

Using the term "apitherapy" on PubMed and the selection "books and documents" no results were retrieved. Therefore, we had to look for different search strategies.

On bookseller platforms and the JUSTfind system of the Justus-Liebig-University Gießen, Germany, which comprises 337 databases from the EBSCO Discovery Service we identified 131 books on apitherapy. Apart from the search terms "apitherapy", "apitherapie" and "apithérapie" we search for possible book issues by opinion leaders, such as former and

current presidents of the Apimondia Scientific Commission on Apitherapy and presidents of societies for apitherapy. Therefore, we also included one book in Italian because the author was Dr. Mateescu, the current president of Apimondia's commission on apitherapy. In all, 129 books on apitherapy could be obtained and were analyzed regarding the recommendations concerning rheumatoid arthritis. There was no selection of the books except for restrictions to English, French, and German language. An overview of the languages in which the books were published and the countries of origin of the authors are given in Table 1. All books were analyzed in detail for apitherapeutic recommendations regarding rheumatoid arthritis. We are aware of the fact that there are significant contributions published in other languages such as Spanish, Romanian and Russian. However, the main impetus regarding apitherapy and rheumatoid arthritis came from Filip Terč (1844–1917), Charles Mraz (1905–1999), and Bodog F. Beck (1871–1942). Their contributions are included in this work.

Table 1. Authors' nationalities and languages of the various analysed books.

	Authors' nationalities [n; (%)]	Language of the book [n; (%)]
German	52 (40.9)	91 (70.5)
English	8 (6.2)	27 (20.9)
French	14 (10.9)	10 (7.8)
Italian	2 (1.6)	1 (0.8)
USA	23 (17.8)	
Romanian	8 (6.2)	
Austrian	5 (3.9)	
Russian	3 (2.3)	
Bulgarian	3 (2.3)	
Ukrainian	2 (1.6)	
Dutch	1 (0.8)	
Swiss	1 (0.8)	
Lithuanian	1 (0.8)	
Algerian	1 (0.8)	
Yugoslavian	1 (0.8)	
Iraqi	1 (0.8)	
Isrealian	1 (0.8)	

n: Total number

Additionally, we looked at whether there is scientific evidence regarding the use of bee products for rheumatoid arthritis, using PubMed, Scopus, and JUSTfind. We used the

search term 'rheumatoid arthritis' combined with the names of various bee products. All retrieved articles were read in full except for the studies published in languages other than English, German, and French. However, it was not our intention to do a systematic review on the topic. These results were only meant to be compared with the suggestions of the books of holistic apitherapy.

3. RESULTS and DISCUSSION

3.1. Historic Data

In 1888 Filip Terč published a case series of 173 patients who received 39,000 bee stings for rheumatoid arthritis. Later in 1912, his son Rudolf Tertsch summarized the experiences of his father and reported that 82% (544/663) could be cured with the help of bee stings (Terč, 1888; Tertsch, 1912).

3.2. Analysis of Apitherapy Books

Sixty-eight out of 129 books (52.7%) mention the topic of rheumatoid arthritis. From these, there are 44 different recommendations. Among these, the recommendation for bee venom was found 15 times and royal jelly five times. All other recommendations were promoted once or twice (Table 2). Interestingly, in only five books (7.3%) we found detailed recommendations regarding the exact dosage and administration of bee products.

Table 2. Recommendations of apitherapists for the treatment of rheumatoid arthritis.

	Frequency	Percent
Bee venom, bee venom acupuncture	1	1.5
Bee venom	15	22.1
Honey, propolis, bee venom	2	2.9
Propolis, royal jelly, bee venom, bees wax	2	2.9
Honey, propolis, bee venom ointment, bee venom acupuncture, bee venom ultrasound administration	1	1.5
Honey (external use), bee venom, bees wax, oxymel	1	1.5
Honey, bee venom	1	1.5
Honey, honey massage, pollen, perga, royal jelly, bee venom, apilarnil	1	1.5
Honey massage, bee venom	1	1.5
Propolis, royal jelly, bee venom, aromiel	1	1.5

Propolis, propolis ointment, propolis compresses, bee venom, stinging nettle	1	1.5
Propolis, bee venom, aromiel	1	1.5
Royal jelly, bee venom	1	1.5
Bee venom, apipressure with honey, propolis, pollen, perga, royal jelly, bee venom, bees wax and apilarnil	1	1.5
Bee venom, bee venom ointment, bees wax compresses	1	1.5
Bee venom, honey compresses	1	1.5
Bee venom, honey compresses, baths, advice against bee venom ointment	1	1.5
Bee venom, bees wax compresses	1	1.5
Royal jelly	5	7.4
Propolis ointment	2	2.9
Propolis	2	2.9
Pollen	2	2.9
Pollen, tea, baths	2	2.9
Forrest honey	1	1.5
Honey, propolis, propolis ointment and tea	1	1.5
Honey, propolis, pollen, perga, royal jelly, bees wax, apilarnil, chitosan	1	1.5
Honey, propolis, propolis ointment, royal jelly	1	1.5
Honey, diet	1	1.5
Honey, cinnamon	1	1.5
Honey massage	1	1.5
Honey massage, diet	1	1.5
Honey compresses, camphor	1	1.5
Honey bath, honey with plant additives (juniper berries)	1	1.5
Propolis ointment, tree gum	1	1.5
Propolis, pollen, propolis compresses, baths	1	1.5
Propolis, royal jelly	1	1.5
Propolis, bees wax	1	1.5
Propolis compresses	1	1.5

Royal jelly, propolis combined with royal jelly	1	1.5
Royal jelly, diet baths	1	1.5
Royal jelly, bee venom ointment, homoeopathy – bee venom	1	1.5
Royal jelly, bee venom ointment, bee cellular therapy, honey compresses	1	1.5
Bee venom ointment, bee venom embrocation	1	1.5
Bee venom ointment, honey compresses, propolis ointment, bees wax packing	1	1.5
Total	68	100.0

As Figure 1 shows, the early publications of Terč (1888) and Tertsch (1912) should have allowed all authors who cover the topic of rheumatoid arthritis to mention bee venom. It is comprehensible that all books published in the 20th century did not mention apipuncture, the combination of bee stings, and acupuncture.

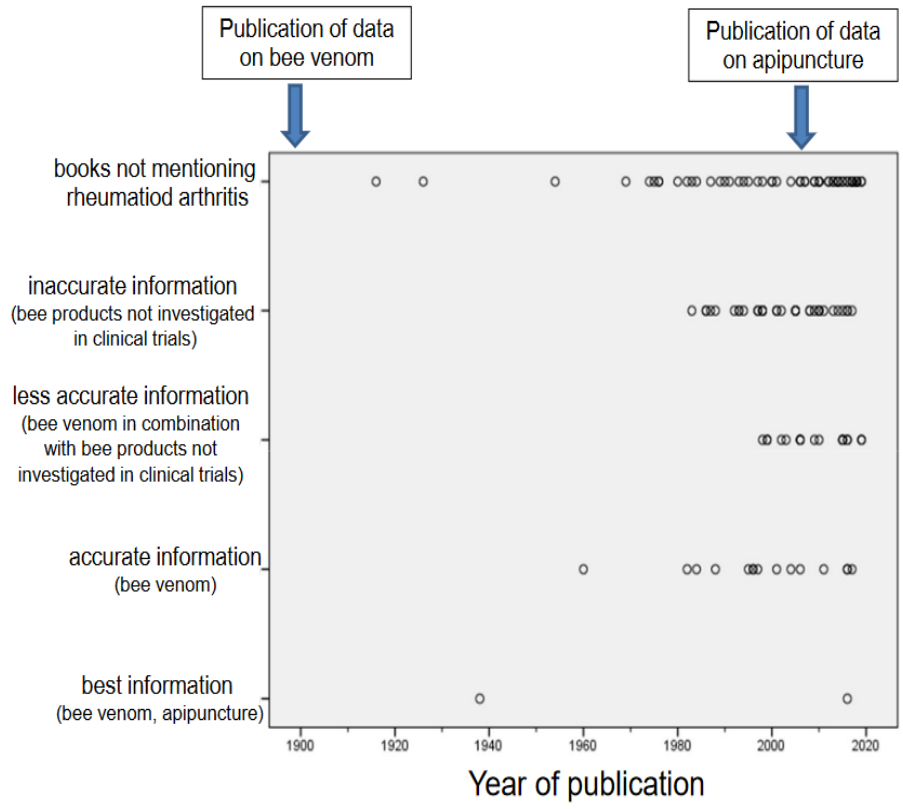

Figure 1. Correctness of apitherapeutic publications depending on the year of publication

3.3. Analysis of the Scientific Literature

The search on PubMed, Scopus, and JUSTfind did not reveal any relevant publications on the topic of rheumatoid arthritis and bee products except for bee venom. Thus, to the best of our knowledge, there are no works, in vitro studies, animal trials, or clinical trials on honey, pollen, propolis, royal jelly, beeswax, apilarnil, and all other bee products. The only study which used honey was an ayurvedic study that used Sidh Makardhwaj, an ayurvedic formulation on the basis of *swarna* (gold), *parada* (mercury), and *gandhaka* (sulphur), which was administered with honey (Kumar et al., 2015). This study was not analyzed in detail because honey was not the main focus of the study. However, recent work suggests that some bee products (honey, propolis) could positively influence the disease (Jagua-Gualdrón et al., 2020). However, this conclusion is only derived from the positive effects of bee products in the treatment of other diseases than RA, and clinical evidence is lacking. Due to the lack of clinical trials on any bee product except bee venom, it is not possible to do a systematic review on apitherapy. The evidence regarding bee venom is described below.

3.4. Evidence Regarding the Use of Bee Venom and Bee Venom Acupuncture (Apipuncture)

The literature search using PubMed, Scopus, and JUSTfind identified basically two fields of interest: bee venom and the combination of bee venom with acupuncture, also called apipuncture, which means that bee stings are applied to the respective acupuncture points.

3.5. Use of Bee Venom

Apart from the reports by Filip Terč and his son, there are few clinical trials on the subject. In 1966 a study of 50 cases was presented, which reported an 84% benefit for bee venom therapy (Steigerwaldt et al., 1966). Apart from this study, there is only in vitro data on the subject. It seems that melittin exerts multiple positive effects on various pathways resulting in a potent anti-arthritis and anti-inflammatory effect by inhibiting sodium nitroprusside, IKK activity, IkB release, the activation of NF-kB, and inflammatory mediators such as iNOS, COX-2, NO, and PEG2, and inactivating the JNK pathway (Zhang et al., 2018).

3.6. Bee Venom Acupuncture

In 2014, Lee and co-workers undertook a systematic review and concluded from one eligible randomized, controlled trial that compared with placebo, bee venom acupuncture may effectively improve joint pain, swollen joint counts, tender joint counts, erythrocyte sedimentation rate, and C-reactive protein, but was not shown to improve morning stiffness

(Lee et al., 2014). Another clinical trial was not included in the systematic review for reasons that we cannot explain (Lee et al., 2014). This study, which assessed five treatment options in 75 patients, concluded that bee venom is an effective treatment for rheumatoid arthritis because it has anti-inflammatory properties with the inhibition of nitric oxide and prostaglandin production (Abdel-Rahman et al., 2013).

Another trial not included in the systematic review is that by Liu et al. (2008) which compared bee venom acupuncture in combination with methotrexate, sulfasalazine, and meloxicam (Western medicines) versus methotrexate, sulfasalazine, and meloxicam only and found that the combined application of bee venom therapy and medication is superior to the simple use of medication. The authors consider that the bee-sting therapy may allow a dose reduction of Western medicines and lower relapse rates (Liu et al., 2008).

Recently another Chinese trial compared apipuncture to standard therapy and found improvements regarding the duration of morning stiffness, arthralgia index, swollen joint count index, joint tenderness index, 15-minute walking time, and various other parameters, with no differences between the groups. The authors found no differences between bee venom acupuncture and standard therapy (Chen et al., 2018). Apart from this clinical study, there have been only animal trials and a case report that provide evidence for the use of bee venom (Tekeoglu et al., 2016; Yamasaki et al., 2015; Zhao et al., 2016).

3.7. Comparison of Apitherapeutic Recommendations and Clinical Evidence

In summary, the current scientific data provide evidence that only bee venom and bee venom acupuncture could be reasonable treatment options for rheumatoid arthritis. As mentioned in the introduction, acupuncture alone could be a reasonable treatment option (Phang et al., 2018).

There is no evidence whatsoever regarding any other bee product. In this respect, only recommendations of bee venom or bee venom acupuncture can be considered reasonable. Therefore, only one book (1.5%) by Hainbuch may be considered to provide the most accurate information mentioning both apipuncture and bee venom, whereas 15 books (22.0%) mention bee venom only Hainbuch, 2016. Recommendations that include bee venom must be considered of little accuracy since the co-administration of bee products may cause ‘drug’ interactions and result in side effects due to the bee products (18 books, 26.5%). Recommendations that do not include bee venom or apipuncture must be considered inaccurate (31 books, 45.6%).

This work shows that the vast majority of recommendations issued in apitherapeutic books must be considered inaccurate or of little accuracy when compared with the scientific

evidence. As shown, there is no scientific background for the use of honey, aromiel, apipressure with honey, propolis (including ointment and compresses), royal jelly, beeswax, oxymel, honey massage, pollen, perga, apilarnil, chitosan, and bee cellular therapy for the treatment of RA. There is the only evidence on bee venom and bee venom acupuncture (apipuncture). Therefore, recommendations of apitherapists must be regarded with great caution. Their practices are not evidence-based and possibly unsafe.

Acknowledging the fact that Terč published his observations in the 19th century and that bee venom acupuncture first became popular at the beginning of the 21st century it is clear that not all books could have provided the optimal information regarding bee venom and apipuncture. However, the question remains why a considerable number of books that mention the topic of rheumatoid arthritis recommend one or more bee products that have never been investigated in this context and often do not mention bee venom and apipuncture despite scientific data. This question cannot be answered by this study. However, the great variety of recommendations shows that there is no uniform treatment concept behind holistic apitherapy. The recommendations appear to be arbitrary and it seems that apitherapists have not compared their recommendations with the results of scientific investigations. This calls for the necessity of education of apitherapists.

However, even for bee venom and bee venom acupuncture, there are several problems that need to be solved before both can be put into clinical practice:

1. Can bee venom be regarded as clinically efficient for the treatment of rheumatoid arthritis?
2. Is bee venom acupuncture superior to bee venom treatment alone?
3. Should bee venom be used in the light of its potential allergic side effects?

3.8. Can Bee Venom Be Regarded As Clinically Efficient For The Treatment of Rheumatoid Arthritis?

Most studies indicate that bee venom and bee venom acupuncture could be interesting treatment options (Lee et al. 2014). Systematic reviews and meta-analyses for other diseases have also confirmed the efficacy of bee venom. These diseases include post-stroke shoulder pain, musculoskeletal pain, and acne vulgaris (Coao et al., 2005; Lee et al., 2008; Lim & Lee, 2015). In particular, the positive effects on post-stroke shoulder pain and musculoskeletal pain allow the conclusion that there are common working mechanisms responsible for positive effects.

3.9. Is Bee Venom Acupuncture Superior to Bee Venom Treatment Alone?

To answer the question, it is important to understand the effects of acupuncture. A meta-analysis on hot flushes in menopausal women with breast cancer concluded that there is insufficient evidence to affirm the effectiveness of traditional Chinese acupuncture compared to sham acupuncture and that there may be slight superiority in the effectiveness of traditional Chinese acupuncture (Lopez-Júnior et al., 2016). Another review confirmed that many clinical trials and experimental studies show that sham acupuncture is as effective as traditional Chinese acupuncture (Zhang et al., 2016). This review concluded that it is important to set standards for acupuncture studies in the future before firm conclusions on the efficacy of acupuncture can be drawn (Zhang et al., 2016). Likewise, it is important that future randomized trials on apipuncture will have an appropriate comparative arm in order to meet current scientific standards.

3.10. Should Bee Venom Be Used in The Light of its Potential Allergic Side Effects?

Treatment with bee venom is associated with the risk of an allergic reaction. According to an analysis by Park et al., bee venom acupuncture shows a 261% increased relative risk for the occurrence of adverse events compared to saline in randomized controlled trials (Park et al., 2015). However, the authors were not sure whether this risk is over-or underestimated because of poor reporting quality in the included studies. As shown, there is a wide range of possible side effects after treatment with bee stings. These include ulnar nerve injury, immune thrombocytopenia, Guillain-Barré syndrome, hepatotoxicity, and many others (Abdulsalam et al., 2016; Alqutub et al., 2011; Lee et al. 2015; Park et al., 2017). To reduce these problems, the use of sweet bee venom, which is comprised of mellitin only, was suggested. However, systemic hypersensitive reactions have already been reported with this concept (Jo & Roh, 2015).

3.11. Limitations

Since we were able to analyze only books in English, French, and German language we may have missed books published in other languages. However, books from famous apitherapists from Russia, Romania, and other countries have been translated into English, French, and German, as indicated in Table 1. Thus, we believe that we did not miss relevant publications. Furthermore, we are aware of the fact that the current practices of apitherapists may differ from what is written in the books. It is also possible that we missed publications on apitherapy and bee products regarding RA which were not listed in the referred search engines.

4. CONCLUSION

According to this analysis, the vast majority of apitherapeutic books do not provide adequate information. Use of the bee products honey, aromiel, apipressure with honey, propolis (including ointment and compresses), royal jelly, beeswax, oxymel, honey massage, pollen, perga, apilarnil, chitosan, and bee cellular therapy cannot be recommended for the treatment of RA. Also, the usefulness of bee products together with other methods and procedures has not yet been shown in clinical studies, as well as an integrative approaches. This negative recommendation is not only because of a lack of scientific evidence but also due the fact that bee products are frequently associated with allergic reactions. Overall, there is evidence that bee venom could be an interesting means of treatment of rheumatoid arthritis. However, especially bee venom is frequently associated with allergic reactions which will limit its use. As shown, bee venom must be considered effective for the treatment of several conditions, e.g. low back pain and post-stroke pain (Lim & Lee, 2016; Shin et al., 2012). However, more and higher quality clinical studies are necessary in order to establish its value for RA either alone or in combination with acupuncture (apipuncture).

DECLARATIONS

The author declares that has no conflicts of interest.

REFERENCES

Abdel-Rahman, M., Elebiary, A. S., Hafez, S. S., Mohammed, H. E., Abdel –Moneim, A. E (2013). Therapeutic activity of BEE-stings therapy in rheumatoid arthritis causes inflammation and oxidative stress in female patients. *International Journal of Research in Ayurveda and Pharmacy*, 4, 316-321.

Abdulsalam, M. A., Ebrahim, B. E., & Abdulsalam, A. J. (2016). Immune thrombocytopenia after bee venom therapy: a case report. *BMC Complementary and Alternative Medicine*, 6, 107.

Aletaha, D., Neogi, T., Silman, A. J., Funovits, J., Felson, D. T., Bingham, C. O., …….& Hawker, G. (2010). Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatology*, 62, 2569-2581.

Alqutub, A. N., Masoodi, I., Alsayari, K., & Alomair, A. (2011). Bee sting therapy-induced hepatotoxicity: a case report. *World Journal of Hepatology*, 3, 268-270.

Bhalerao, M. S., Bolshete, P. M., Swar, B. D., Bangera, T. A., Kolhe, V. R., Tambe, M. J., Wade, M. P., Bhowate, S. D., Sonje, U. B., Gogtay, N. J., & Thatte, U. M. (2013). Use of and satisfaction with complementary and alternative medicine in four chronic diseases: a cross-sectional study from India. *National Medical Journal of India*, 26, 75-78.

Cao, H., Yang, G., Wang, Y., Liu, J. P., Smith, C. A., Luo, H., & Liu, Y. (2005). Complementary therapies for acne vulgaris. *Cochrane Database of Systematic Reviews*, 1, CD009436.

Chen, J., & Lariviere, W. R. (2010). The nociceptive and anti-nociceptive effects of bee venom injection and therapy: a double-edged sword. *Progress in Neurobiology*, 92, 151-183.

Chen, S. Y., Zhou, P., & Qin, Y. (2018). Treatment of rheumatoid arthritis by bee-venom acupuncture. *Zhen Ci Yan Jiu*, 43: 251-254.

Fernández-Llanio Comella, N., Fernández Matilla, M., & Castellano Cuesta, J. A. (2016) Have complementary therapies demonstrated effectiveness in rheumatoid arthritis? *Reumatología Clínica*, 12, 151-157.

Fiehn, C., Holle, J., Iking-Konert, C., Leipe, J., Weseloh, C., Frerix, M., Alten, R., Behrens, F., Baerwald, C., Braun, J., Burkhardt, H., Burmester, G., Detert, J., Gaubitz, M., Gause, A., Gromnica-Ihle, E., Kellner, H., Krause, A., Kuipers, J. 0., …….. & Krüger, K. (2018) S2e-Leitlinie: Therapie der rheumatoiden Arthritis mit krankheitsmodifizierenden Medikamenten. [S2e guideline: treatment of rheumatoid arthritis with disease-modifying drugs]. *Zeitschrift für Rheumatologie*, 77(Suppl 2), 35-53.

Hainbuch, F. (2016). Bienengiftbuch – Akupunktur mit Bienengift und Bienenstichen Leipzig. (Einbuch).

Institute for Quality and Efficiency in Health Care. Systematic guideline search and appraisal, as well as extraction of relevant recommendations, for a DMP "Chronic Back Pain" [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2015 Nov. Extract of Final Report No. V14-04.

Jagua-Gualdrón, A., Peña-Latorre, J. A., & Fernadez-Bernal, R. E. (2020). Apitherapy for osteoarthritis: perspectives from basic research. *Complementary Medicine Research*, 27, 184-192.

Jo, N., & Roh, J. (2015). Systemic immediate hypersensitive reactions after treatment with sweet bee venom: a case report. *Journal of Pharmacopuncture*, 18, 59-62.

Kumar, G., Srivastava, A., Sharma, S. K., Rao, T. D., & Gupta, Y. K. (2015). Efficacy & safety evaluation of Ayurvedic treatment (Ashwagandha powder & Sidh Makardhwaj) in rheumatoid arthritis patients: a pilot prospective study. *Indian Journal of Medical Research*, 141, 100-106.

Lee, H. J., Park, I. S., Lee, J. I., & Kim, J. S. (2015). Guillain-Barré syndrome following bee venom acupuncture. *Internal Medicine*, 54, 975-978.

Lee, J. A., Son, M. J., Choi, J., Jun, J. H., Kim, J. I., & Lee, M. S. (2014). Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials. *BMJ Open*, 4, e006140.

Lee, M. S., Lee, M. S., Yang, C. Y., Lee, S. I., Joo, M. C., Shin, B. C., Yoo, W. H., & Shin, Y. I. (2008). Use of complementary and alternative medicine by rheumatoid arthritis patients in Korea. *Clinical Rheumatology*, 27, 29-33.

Lee, M. S., Pittler, M. H., Shin, B. C., Kong, J. C., & Ernst, E. (2008). Bee venom acupuncture for musculoskeletal pain: a review. *Journal of Pain*, 8, 289-297.

Lim, S. M., & Lee, S. H. (2015). Effectiveness of bee venom acupuncture in alleviating post-stroke shoulder pain: a systematic review and meta-analysis. *Journal of Integrative Medicine*, 13(4), 241-247.

Littlejohn, E. A., & Monrad, S. U. (2018). Early diagnosis and treatment of rheumatoid arthritis. *Primary Care*, 45, 237-255.

Liu, X. D., Zhang, J. L., Zheng, H. G., Liu, F. Y., & Chen, Y. (2008). Clinical randomized study of bee-sting therapy for rheumatoid arthritis. *Zhen Ci Yan Jiu*, 33(3), 197-200.

Lopes-Júnior, C. L., Cruz, L. A., Leopoldo, V. C., Campos, F. R., Almeida, A. M., & Silveira, R. C. (2016). Effectiveness of Traditional Chinese Acupuncture versus sham acupuncture: a systematic review. *Revista Latino-Americana de Enfermagem*, 24, e2762.

Park, J. H., Yim, B. K., Lee, J. H., Lee, S., & Kim, T. H. (2015). Risk associated with bee venom therapy: a systematic review and meta-analysis. *PLoS One*, 10, e0126971.

Park, J. S., Park, Y. G., Jang, C. H., Cho, Y. N., & Park, J. H. (2017). Severe ulnar nerve injury after bee venom acupuncture at a Traditional Korean Medicine clinic: a case report. *Annals of Rehabilitation Medicine*, 41, 483-487.

Phang, J. K., Kwan, Y. H., Goh, H., Tan, V. I. C., Thumboo, J., Østbye, T., & Fong, W. (2018) Complementary and alternative medicine for rheumatic diseases: A systematic review of randomized controlled trials. *Complementary Therapies in Medicine*, 37, 143-157.

Shin, B.-C., Kong, J. C., Park, T. Y., Yang, C. Y., Kang, K. W., Choi, S. (2014). Bee venom acupuncture for chronic low back pain: A randomised, sham-controlled, triple-blind clinical trial. *European Journal of Integrative Medicine*, 4, e271-e280.

Steigerwaldt, F., Mathies, H., & Damrau, F. (1966) Standardized bee venom (SBV) therapy of arthritis. Controlled study of 50 cases with 84 percent benefit. *Industrial Medicine and Surgery*, 35, 1045-1049.

Tekeoglu, I., Akdogan, M., & Kaleli, S. (2016). Bee venom apipuncture; a successful therapy for myofascial pain. A case based review. *Journal of Apitherapy*, 1,20-22.

Terč, F. (1888). Ueber eine merkwuerdige Beziehung des Bienenstiches zum Rheumatismus. *Wiener medizinische Presse*, 35, 1261-1264.

Tertsch, R. (1912). Das Bienengift im Dienste der Medizin. Wien (Österreichischer Reichsverein für Bienenzucht - independently published).

Tokem, Y., Parlar Kilic, S., Ozer, S., Nakas, D., & Argon, G. (2014). A multicenter analysis of the use of complementary and alternative medicine in Turkish patients with rheumatoid arthritis: holistic nursing practice review copy. *Holistic Nursing Practice*, 28, 98-105.

Yamasaki, S. C., Mendes, M. T., Alponti, R. F., & Silveira, P. F. (2015). Efficacy of parenteral administration of bee venom in experimental arthritis in the rat: a comparison with methotrexate. *Toxicon*, 98, 75-88.

Zhang, S., Liu, Y., Ye, Y., Wang, X. R., Lin, L. T., Xiao, L. Y., Zhou, P., Shi, G.X., & Liu, C. Z. (2018). Bee venom therapy: potential mechanisms and therapeutic applications. *Toxicon*, 148, 64-73.

Zhang, L. L., Chu, Q., Wang, S., Lai, H., & Xie, B. B. (2016). Is sham acupuncture as effective as traditional Chinese acupuncture? It's too early to say. *Chinese Journal of Integrative Medicine*, 22, 483-489.

Zhao, M., Bai, J., Lu, Y., Du, S., Shang, K., Li, P., Yang, L., Dong, B., & Tan, N. (2016). Anti-arthritic effects of microneedling with bee venom gel. *Journal of Traditional Chinese Medical Sciences*, 3, 256e262.