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The Role of Insects in Medical Engineering and Bionics: Towards Entomomedical Engineering

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***Abstract*—Insects are important agents in ecosystems. Their diverseness and developed coping mechanisms also make them interesting for direct application and as a source of inspiration in medical engineering. We summarized the main contribution of insects in biomedical applications. Medical centers in North America, and Europe use fly larvae for maggot therapy to remove necrotic tissue, decrease infection risk, and improve wound healing. Ant mandibles are used as a suturing technique by African tribes and as sources of inspiration for surgical clamps. Both the mosquito fascicle and the wasp ovipositor are sources of inspiration for the design of medical needles. Herein, a new research field called "*entomomedical engineering,*" is proposed. We define entomomedical engineering as the branch of engineering that uses insects either directly or as a source of inspiration to design and develop medical treatments or instruments. In addition, we want to emphasize the importance of preserving insects because of their function in the ecosystem, medicine, and medical engineering.**

***Index Terms*—Biologically-inspired design, insect, maggot therapy, medical clamp, medical needle.**

I. INTRODUCTION

HUMANS see many insect species as pests, but these organisms play a crucial role in keeping the planet livable [1], [2]. Insects are important providers [3], decomposers [4], pest controllers [5], pollinators [6], soil engineers [7], and more. Insects are a source of food for larger animals including other arthropods, fish, amphibians, reptiles, birds, and mammals. Without insects, species higher up in the food chain suffer from food scarcity [8]. Besides their essential roles in the ecosystem, clinicians and engineers use insects directly and as a source of inspiration [9], [10]. Insects are the most diverse organisms. They are unmatched in their species numbers, biomass, and ecological impact [11]. Their cycle of reproduction resumes quickly, allowing the development of high genetic diversity. They developed characteristics and coping mechanisms to survive in extreme situations, making them attractive sources of direct application and bio-inspiration in medical engineering as bio-engineers. The direct application of insects or insect-derived products in medicine is called entomotherapy [12]–[14]. Insect-derived products such as honey, venom, and insect anticoagulants and their clinical application were described by Rather *et al.* [14]. Insects are used directly in bio-surgery and bio-clamps, which often already started in veterinary or traditional medicine and are recently becoming of increasing interest [15], [16].

Recent studies showed population declines of insect species [17], [18]. Other studies stated that terrestrial insects decline, whereas the number of freshwater insects increased [19]. Montgomery *et al.* [20] argue that most documented collapses of insect species are from geographically restricted studies, which do not allow us to conclude insect species' declines on a global scale. There is a need for greater investigation of insect declines. However, the severity of the reported insect declines calls for immediate action [21]. The primary drivers of insect declines are pollution by pesticides and fertilizers, insect habitat loss and degradation, biological factors such as pathogens and introduced species, and climate change [22].

In this review, we summarize the main contribution of insects in biomedical applications. We included both the insects' direct application in therapies as bio-actuators and the insects' indirect application as a source of inspiration for biomedical tools. Furthermore, we want to emphasize the importance of preserving insects because of their ecological function, as well as of their role in medicine and medical engineering. This review provides an overview of the scientific literature on both the direct application and bio-inspiration of insects in medicine. The first part of this review describes the insects' direct application in medicine, including bio-surgery with maggot debridement therapy (MDT) and bio-clamps. The second part describes the insect-inspired medical devices in the scientific literature: bio-inspired needles and bio-inspired clamps.

II. MATERIALS AND METHODS

To survey the scientific literature of insects used in medicine, we used the Scopus database. The search query

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was a Boolean combination of keywords regarding the following: (1) the type of insect and (2) the target application. In the Scopus search, we used the function "LIMIT TO" to limit the search to English language publications and publications within the "Medicine" and "Engineering" subject areas. We used a separate search query for bio-surgery, bio-clamps (including bio-inspired clamps), mosquito-inspired needles, and wasp-inspired needles. Supplementary file S1 contains the search queries used in this study.

The search resulted in 342 articles from the Scopus database. The title and abstract of the scientific articles were screened based on the eligibility criteria. For the articles about bio-surgery, solely articles describing controlled clinical trials of therapy using alive, disinfected fly larvae, i.e., maggots, were included. We excluded case studies and *in vitro* tests. For the articles on bio-clamps and bio-inspired needles, we included articles describing the mechanical working principle or design. We excluded articles focused on motion planning algorithms, computational modelling, or tissue-needle interaction. We read the full text of the remaining papers and checked the references of the articles included in this review to retrieve relevant articles not captured by the search query in Scopus. In the end, this review encompasses 93 scientific articles.

Fig. 1. Temporal distribution of articles about a clinical study that applies maggot therapy.

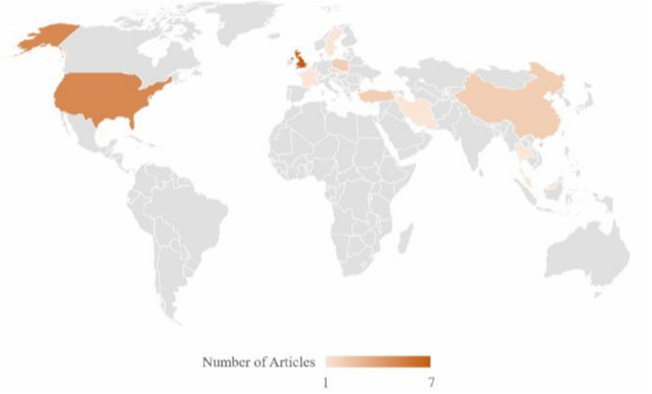

Fig. 2. Spatial distribution of the articles about a clinical study that applies maggot therapy.

III. Direct Application of Insects in Medicine

A. Bio-Surgery

Humans have used insects in skin wound healing for a long time, and our interest in their use has increased in the last years. The definition of bio-surgery is using living maggots to remove necrotic tissue, decrease the risk of infection, and improve wound healing [23], [24]. Other terms used in the scientific literature for bio-surgery are maggot therapy, larval therapy, maggot debridement therapy (MDT), larval debridement therapy, maggot wound therapy, and biodebridement [25]–[28]. Some fly species' larvae feed upon living or decaying animal tissue called myiasis [29], [30]. The Diptera order is the main source of insects in direct bio-surgery applications. Some larvae limit their digestion to dead or necrotic tissue called semi-specific myiasis. These larvae are the ones that are used in bio-surgery. The "greenbottle" blowfly, *Lucilia sericata* Meigen (Diptera: Calliphoridae), is used the most in maggot therapy [31]. Other species often used are *Lucilia illustris* Meigen (Diptera: Calliphoridae) and *Phormia regina* Meigen (Diptera: Calliphoridae) [32]. The maggots produce proteolytic enzymes like collagenase [33], [34]. Collagenase effectively breaks down necrotic tissue to a semi-liquid, which the larvae absorb and digest.

Table I shows a timeline of the history of scientific literature on the use of maggot therapy. Ambroise Paré was the first to observe the beneficial effects of maggots in wounds during the battle of St. Quentin in 1557 [35]. Baer [36] was the first to report a scientific study on the application of maggots to treat chronic osteomyelitis [37]. During World War I, Baer, an orthopedic, found that the wounds of two soldiers swarmed with maggots. The wounds were granulated with no evidence of sepsis. MDT was popular in the 1930s and early 1940s to clean exposed wounds [30]. By the mid-1940s, maggot therapy ceased in popularity, simultaneously with the beginning of the antibiotic era [30], [38]. Antibiotics prevented the spread of infections by bacteria that could lead to soft-tissue complications, which the larvae treated previously [25]. MDT's other main challenges were social approval, local pruritis, the use of sterile maggots, and wounds with copious exudate because then maggots die due to lack of oxygen. For more information about the history of maggot therapy, we refer the reader to [30], [32], [37]–[42].

At the end of the twentieth century, maggot therapy's revival started with the first controlled clinical trials [43]. Also, the treatment of other wounds than osteomyelitis was studied. Clinicians extended MDT to the field of diabetes and land mine wounds in developing nations where access to medical treatment may be inadequate [38], [44]. Figures 1 and 2 show the temporal and spatial distribution of the articles published about a clinical study that applies maggot therapy, respectively. The advantages of maggots caused the revival, as they are (1) active in debriding necrotic tissue, (2) relative safe, (3) simple, (4) efficient, (5) cheap, and (6) effective even in the context of antibiotic-resistant infections [25], [38]. By 2000, MDT was a treatment option in approximately 50 medical centers in North America and the United Kingdom [38]. Furthermore, medical maggots were produced and distributed to 400 medical centers in the United Kingdom, Belgium, Germany, and Sweden [38]. In 2004, the U.S. Food and Drug Administration (FDA) granted market clearance to medicinal maggots as a medical device [45]. The maggot's physical activity is essential for the debridement; therefore, the FDA classified the medical maggots as a medical device instead of a drug [43]. Maggots move over the wound,

TABLE I
SCIENTIFIC LITERATURE ABOUT THE USE OF MAGGOTS IN MEDICINE UNTIL ITS POPULARITY CEASED IN 1940

Time	Event	Reference
1557 – Battle of St. Quentin	Abroise Paré observed the beneficial effects of fly larvae in wounds.	[35]
1929 – Syrian campaign	DJ Larray reported that maggots removed necrotic tissue, while enhancing the granulation of living tissue in the soldiers of Napoleon Bonaparte's army he treated.	[36]
1931 – World War I	Scientific study on the use of maggots for the treatment of chronic osteomyelitis. Method to rear sterile maggots, by first sterilizing the eggs and then raising the maggots on a sterile food source.	[36]
1934	Wound becomes alkaline, because the maggots excrete calcium carbonate.	[145]
1935	MDT is useful in any wound containing sloughing tissue which can be exposed by incision, not only for osteomyelitis. Maggot therapy is the most rapid method to remove sloughing soft tissue after excision.	[146]
1940s	MDT ceased in popularity, simultaneously with the beginning of the antibiotic era.	[30, 38]

MDT = maggot debridement therapy

thereby ploughing the tissue and simultaneously spreading its alimentary secretions and excretions (ASE). The ASE liquefies the necrotic tissue. Afterward, the maggots can imbibe it. Medicinal maggots work through the ASE and the physical contact with the host, inducing debridement, disinfection, growth stimulation, and wound healing. For more information about the maggot-host interactions to achieve these working mechanisms, we refer the reader to [43]. In the Netherlands, the larvae of *L. sericata* were approved as an unregistered medicine in 2014 [46]. In Germany, there were 5017 cases of MDT in 2016 [47]. Other countries where MDT is reintroduced are Israel, the United Kingdom, Sweden, Switzerland, Ukraine, and Thailand [47]. Supplementary file S2 presents clinical studies of wound treatment with maggots (*L. sericata*, unless otherwise specified). The studies in S2 show that the maggots' debridement efficacy is beyond doubt, yet the disinfection and growth stimulation activity remains questionable [43]. Sherman [43] stated we need more clarity regarding MDT's role in promoting wound closure. Maggots' physical effects do not last longer than a few weeks after MDT ended. If the wounds do not heal immediately, there is the risk for recolonization, infection, stagnation, and necrosis.

B. Bio-Clamp

Closing a wound using ant mandibles of large black ants is described as one of the first suturing techniques [48]–[54]. The insects family Formicidae of the order Hymenoptera is the main source of insects in direct bio-clamp applications. The clinician lets multiple ants bite the wound edges and pull them together [48], [49], [51]–[53]. Afterward, the ants' bodies are twisted off or cut off, leaving the head with the mandibles to maintain the edges close together [48], [49], [51]–[53]. Supplementary file S3 contains a timeline of the reported use of ants as a suturing technique. Schiappa and Van Hee [52] stated that ancient populations in various continents used giant ants like *Oechylla smaragdina* (Fabricius) and *Eciton burchelli* (Westwood) as a suturing device. These ants have powerful claws that can draw the edges of a wound together by biting them. Iavazzo *et al.* [53] stated that different ant species were used in different parts of the world, amongst them *Atta cephalotes* (Linnaeus), *Eciton burchellii* (Westwood), and *Oecophylla smaragdina* (Fabricius). Nowadays, ant mandibles are used as a suturing technique by some African tribes [51].

IV. INSECTS AS INSPIRATION MODELS IN MEDICAL ENGINEERING

Mechanical failure in guidewires and needle-like instruments are often caused by buckling. To prevent buckling, either the penetration tool's critical load can be increased, or the substrate's penetration load can be decreased [55]. Sakes *et al.* [55] stated that the mosquito proboscises and wasp ovipositors are examples from nature that combine different buckling prevention strategies. The insect orders Diptera and Hymenoptera are the main sources of inspiration in bio-inspired needles.

A. Mosquito-Inspired Microneedles

Microneedles are used for minimally invasive medical treatments like sampling blood or subcutaneously medication delivery [56], [57]. The microneedle allows for precise localization of the medication to obtain effective absorption into the bloodstream [58]. An example of an application field for microneedles is self-monitoring of blood glucose for diabetes patients [59]. The mosquito proboscis, the mouthparts of the female mosquito that she uses to suck up blood, is reported as a source of inspiration to design advanced microneedles [60]. The mosquito's biting process and its different phases were detected electronically by Kashin and Wakely [61] and Kashin [62]. The mosquito (*Aedes albopictus* Skuse) was used as an electrical switch where electrical conduction was achieved only when there was penetration. Ramasubramanian *et al.* [63] used high-speed video imaging to study the fascicle insertion of the *Aedes aegypti* (Linnaeus) mosquito species. The female mosquito can penetrate the skin with a flexible needle that is small and flexible and can draw blood. In contrast, human-made polymeric microneedles are often not stiff enough to penetrate the skin without buckling. High-speed video images showed that the frequency of the head lateral movement decreased from 15-17 Hz in the beginning to 6 Hz towards the middle to end of the penetration. The authors presented an analytical study using a mathematical model where the fascicle is modeled as a slender column supported on an elastic foundation, subjected to nonconservative and conservative loads at the end. The authors concluded that the lateral support of the labium and the nonconservative loads help the mosquito fascicle penetrate the skin. Kong and Wu [60] studied the *A. albopictus* (Skuse) mosquito species to investigate the mechanical insertion force of the fascicle into the skin using scanning electron microscope imaging and high-speed video imaging. Experimental results showed that in the early stages of penetration, the maxilla frequency is 10-15 Hz. This is reduced to 6-8 Hz at half depth to 3-5 Hz in the last stages of the penetration process. These maxilla frequencies comply with the results reported by Ramasubramanian *et al.* [63]. The penetration time was 10-20 s; suction time was 2-3 min; the quantity of sucked blood was about 3 mg. The measured insertion force range is 6-38 μN, with a mean value of 16.5 μN, three orders of magnitude smaller than the reported minimum insertion force to penetrate human skin. This is explained by the variable frequency saw-like maxillae that cut into the tissue of the skin.

Oka *et al.* [64] were first to develop a hollow microneedle inspired by the mosquito proboscis, with a jagged shape inspired by the mosquito's maxillae to ease cutting and decrease the contact area between the needle and the cutting surface. The authors manufactured a silicon microneedle with a jagged shape, reinforced with polycrystalline silicon with a length of 1 mm and an outer diameter of 85 μm, used for trace blood tests in diabetes patients. An insertion force of 14.7 mN was found to be sufficient to penetrate the skin.

Izumi *et al.* [65] developed electrochemically etched silicon needles with cooperative motions in a parallel configuration, imitating the mosquito labium and two maxillae. Experimental results showed that cooperative motion resulted in a puncture force of 58.8 mN, compared to 205.9 mN for no motion. The authors also developed a polylactic acid (PLA) needle, considering medical applications, because PLA is biodegradable, non-brittle, and flexible, preventing possible broken pieces from remaining in the body. The PLA and silicon needles showed comparable piercing forces. Polymers like the biodegradable PLA are considered the most promising materials for microneedle fabrication due to their favorable biocompatibility [66].

Similar jagged-shaped microneedles are presented in a number of other studies, made from PLA [67], [68], silicon [69], [70], stainless steel [71], [72], and tungsten with a biocompatible coating [57]. A jagged-shaped, vibrated microneedle made from PLA is presented in [73]. Jagged-shaped vibrated microneedles that consist of multiple parallel segments are presented in a number of other studies, made from PLA [74], silicon [75], silicon with a biocompatible coating [76], photocurable epoxy resin [77], ceramic [78], and a frequency-dependent viscoelastic material [79]. Smooth-surface vibrated microneedles made from silicon [58] or titanium for a micro pumping device are presented in a number of other studies [59], [80]–[82]. Other mosquito-inspired smooth-surface microneedles are presented in a number of other studies, made from stainless steel [83], silicon [84], and shape memory polymer [85].

B. Wasp-Inspired Steerable and Self-Propelling Needles

The ovipositor is a tube-like organ that the wasp uses for egg-laying. Sakes *et al.* [55] stated that the Hymenoptera ovipositor combines multiple buckling prevention strategies. For Hymenoptera, the ovipositor is a piercing organ, comprising three separate pieces, capable of penetrating different materials such as wood. In order to increase the critical buckling load, the ovipositor shows amongst others the following characteristics: (1) it contains metal ions manganese and zinc that increases the bending stiffness [86], (2) the internal morphology retains the circular cross-section during penetration, this keeps the second moment of area high [55], (3) it shows barbed anchoring, which decreases the effective-length factor [60], (4) the ovipositor of Hymenoptera *Megarhyssa nortoni* (Cresson) is supported by "a longitudinal median groove flanked by series of tubercles" [87], and (5) it uses reciprocating penetration [88]. The barbed anchoring and reciprocating penetrating motion are strategies that also facilitate the penetration of the mosquito proboscis [63], [74]. Besides the buckling prevention strategies, the three longitudinal segments of the ovipositor allow for a reorientation of the ovipositor tip to a bevel-shaped tip [89], [90]. By antagonistic movements of the ovipositor segments, steering is possible. The ovipositor moves without rotation around the long center axis [91]–[93], causing less strain to the surrounding material [94]. Conventional instruments used for minimally invasive (MI) surgical interventions follow a straight-line trajectory, which reduces the planning choices of the surgeon [95]. The steering capabilities of the ovipositor of Hymenoptera make it an interesting source of inspiration for a probe capable of steering along a curved path. Neurosurgery is one field of application for steerable needles. Other fields are soft tissue applications, e.g., brachytherapy, core needle biopsy, and drug delivery. Soft tissue applications require the outer needle diameter to be below 2 mm (14 Gauge) [89], [96], [97]. Besides steerable needles, the Hymenoptera ovipositor also inspired the design of devices such as planetary and earth drills [98]. In this section, we examined some scientific publications that presented their development of steerable needles inspired by Hymenoptera.

Researchers from the Imperial College London worked on designing a steerable needle inspired by the Hymenoptera ovipositor [99]–[105]. They studied the penetration mechanism of the wasp's ovipositor, the interlocking mechanism of the ovipositor segments, and the surface texture of the ovipositor. Frasson *et al.* [95] designed a probe to access deep brain lesions through curved trajectories. The probe consists of two parallel segments with an interlocking mechanism similar to the olistheter in the Hymenoptera ovipositor, which interconnects the three segments the ovipositor consists of. The probe was produced using 3D printing and had an outer diameter of 4.4 mm. The two segments are actuated independently. When one of the segments is moved, off-axis reaction forces cause the segment to deflect in the bevel direction. The other segments follow the curved trajectory laid out by the first segment; this allows two-dimensional steering. Similar steerable probe designs consisting of two parallel needle segments were presented in a number of other studies [106]–[108]. Burrows *et al.* [109] developed a probe prototype made of a novel composite structure of alternating rigid and soft sections produced using 3D printing. The rigid sections are located at the interlocking sections and add strength to this mechanism. The soft regions are located in

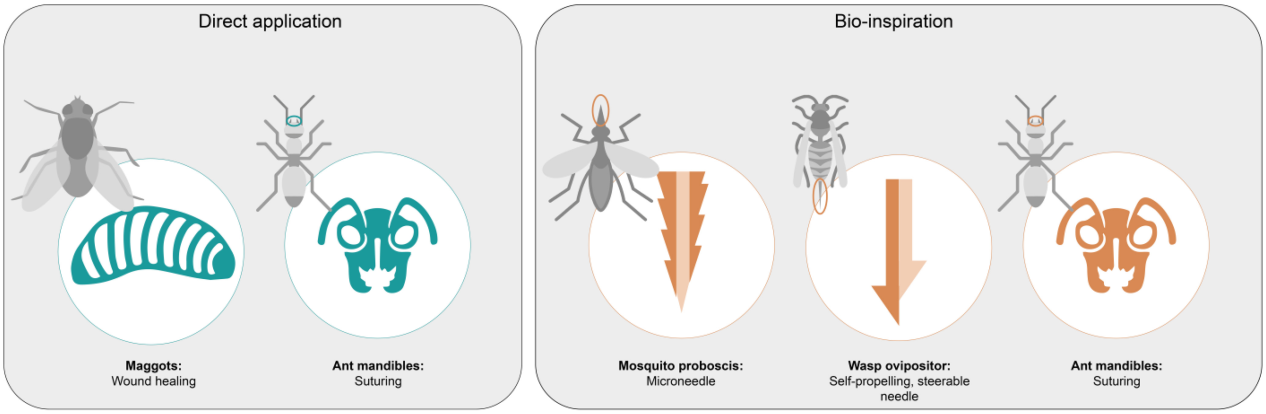

Fig. 3. Visual representation of the direct application and bio-inspiration of insects in medicine described in this review.

the regions between the rigid sections and allow the prototype to remain flexible. The needle consists of four parallel needle segments and has an outer diameter of 4 mm. Experiments in 4.5%wt gelatin showed the capability of steering in 3D with a mean positional error of 0.46 mm and an approach angle error of 1.05°. Similar steerable probe designs consisting of four parallel needle segments with a focus on the cross-section geometry [110], [111], on the composite body structure, on the control system for steering [94], [112], [113], on 3D steering [114], on the probe-tissue interaction [115], or on the integration with a laser Doppler system [116] have also been reported.

Sprang *et al.* [117] developed a smooth-surface four-segment prototype inspired by the Hymenoptera ovipositor. The authors stated that the ovipositor contains serrations that induce friction, which might cause unwanted tissue damage in a medical application. Therefore, they produced a multi-segment needle without gripping textures that could penetrate tissue with a low net push force. Scali *et al.* [89] decided to step away from nature with the interlocking mechanism and instead used an interlocking ring [89], [118] or a 10-mm piece of thin-walled shrinking tube [119] in combination with off-the-shelf Nitinol rods. Since no interlocking mechanism had to be produced, a tip diameter of up to 0.4 mm could be obtained. This is thinner than the other ovipositor-inspired needles in literature, where the outer diameter ranges between 4 and 12 mm [94], [95], [108], [109], [111], [113], [114]. One or two rods were actuated simultaneously, whereas the remaining stationary rods generated a friction force to compensate for the friction and cutting force of the advancing wires. Experimental evaluation of the 1.2-mm diameter prototype with an interlocking ring [89] in 4%wt gelatin showed that the needle required no external push force and allowed steering through the bevel-tip. The resultant steering curvature was 0.000184 mm-1, and the deflection-to-insertion ratio was 0.0778, which is lower than previously reported steering performances [94], [108], [114], possibly due to bifurcation of the wires.

C. Bio-Inspired Clamp

The insect family Formicidae of the order Hymenoptera is the main source of inspiration in bio-inspired clamps. Brito *et al.* [120], [121] designed a surgical clamp inspired by the *Atta laevigata* (Smith) ant. The aim of the clamp is to make placement and removal of the clamp more efficient and less traumatic for the patient. The clamp consists of a handle structure used to open the clamp and a system in contact with the skin. The working mechanism of the surgical clamp mimics the ant mandibles: (1) an external compressive stress must be applied to the levers to open the clamp, (2) the surgical clamp can penetrate the skin due to elastic forces, (3) the clamp falls by itself after healing, which relieves the inconvenience of the clip removal process. Brito *et al.* [120] studied the mandibles of the *A. laevigata* ant to present a selection of candidate biocompatible materials for surgical clamps. The biological materials of insects' mandibles can be correlated with polymers because the mandibles are composed of waxes, polysaccharides, and proteins. Nanoindentation measurements showed that the hardness in the internal and external regions was 0.36 ± 0.06 GPa and 0.19 ± 0.04 GPa, respectively and the elastic modulus 6.16 ± 0.23 GPa and 2.74 ± 0.44 GPa, respectively. Atomic force microscopy (AFM) showed an average roughness of 6.73 ± 0.90 nm and 11.87 ± 1.42 nm, respectively. Zinc and manganese in the internal region justify the increase of hardness and elastic modulus in this region [86]. The authors concluded that appropriate materials for the surgical clamps include PLA, polycaprolactone, or polyglycolide acid, possibly in combination with natural polymers as chitin, collagen, or fibroin. For the handle structure, metallic biomaterials as stainless steels and titanium alloys are proposed. In another study, Brito *et al.* [121] studied the geometry and material selection of the biomimetic surgical clip using the finite element method (FEM) in ANSYS. AISI 316L and AISI 420 stainless steel were selected for the stress and strain analyses. The locations with the highest stress concentrations were determined, FEM results showed plastic deformation and possible rupture [121]. The results indicate that either the design's geometry needs optimization or the needle design should be made out of ferritic and martensitic stainless steel [121].

V. DISCUSSION

Figure 3 shows a schematic overview of the direct application and bio-inspiration of insects used in medicine and medical engineering, respectively, described in this review.

This review also describes the direct application of maggots for wound healing. The FDA approved the medicinal maggots in 2004 and approved a preassembled version, including a netting cage in 2007 [45]. Nevertheless, treatments directly applying insects, e.g., maggot therapy, face the challenge of social approval. The poor acceptance by both patients and clinicians hinders the utilization of maggots in medicine [122]. Raising the awareness about maggot therapy and adequate psychological preparation for the patients undergoing maggot therapy might alleviate concerns about the treatment and might increase its social approval. Another method would be to extract the working principle of the maggots for medical application. During the 1930s, Livingston [123] attempted to isolate the larvae's active principle in a maggot extract. The vaccine was abandoned because of significant systemic reactions. Sherman [42] stated that someday maggot-derived products might replace live maggot larvae for wound care, e.g., antimicrobial agents capable of suppressing methicillin-resistant *Staphylococcus aureus* [124], [125]. Čeřovský *et al.* [124] stated that lucifensin is assumed to be the key component that protects maggots in the infectious environment of the wound during MDT and is believed to be effective against pathogenic elements in the wound such as methicillin-resistant *Staphylococcus aureus*. The authors reported the presence of lucifensin in the gut, salivary glands, fat body, and hemolymph of the *L. sericata* larvae. Lucifensin was also detected in the washes of maggot larvae removed from the wound of a diabetic patient. Mass spectrometry and reversed-phase high-performance liquid chromatography showed the anti-*Micrococcus luteus* (Schroeter) activity of lucifensin. Andersen *et al.* [126] tried to identify the antibacterial mechanism in maggots and to purify the components that could be used in medicine. The authors stated they did not find an obvious protein with antimicrobial activity, so the authors could not pinpoint lucifensin as the key component that is effective against pathogenic elements. This is in contrast with the results of Čeřovský *et al.* [124]. Lucifensin showed to be active against Gram-positive bacteria, whereas no antimicrobial activity towards Gram-negative bacteria was shown. The authors stated that in future studies, the expression of lucifensin at different maggot instars should be validated in order to evaluate whether lucifensin is responsible for the antimicrobial activity in maggot excretions and secretions. In 1995, Morgan [30] already stated an opportunity to develop genetically engineered flies bred in a sterile environment. Linger *et al.* [127] presented a novel concept that combines MDT benefits with genetic engineering to promote wound healing. The authors investigated human platelet-derived growth factor-BB as a potential treatment for non-healing wounds, as it is known to promote wound healing [128]. The authors produced genetically modified *L. sericata* larvae that secrete platelet-derived growth factor-BB at a detectable level in maggot ASE. The effector genes could be other growth factors such as lucifensin. This would indicate that ASE would be active against Gram-positive bacteria [124].

Mosquitoes and wasps are both capable of penetrating solid substrates. In the scientific literature, two common biological features were described that facilitate the needle insertion, the serrated needle segments and the reciprocating motion of the needle segments [129]. Besides the mosquito proboscis and the wasp ovipositor, other parts of insects used as inspiration for the design of medical needles are the mouthpart of the tsetse fly [130], [131], the mouthpart of Cicadellidae [132], the spine of the caterpillar [133], and stings of honey bees and paperwasps [134]. For future research, it is interesting to look into the mechanical differences of the medical needles inspired by these different insects. Besides the insects and insect-inspired products described in this review, other insects and insect-derived products are used in folk healing that might have potential in conventional medicine. Cherniack [16] wrote a review of the use of insects and insect-derived products in folk healing. Besides maggot therapy, the author included honey treatment, the use of royal jelly, and the application of bee and ant venom and blister beetle-derived cantharidin. Honey is used to heal wounds or treat burns [135]. Royal jelly is used to treat postmenopausal symptoms [136]. Bee and ant venom is used to treat swollen joints in patients with rheumatoid arthritis [137]. Blister beetle-derived cantharidin is used to treat warts and molluscum [138]. The *Decticus verrucivorus* (Linnaeus), also called the wart-biter, has gotten its name from the old Swedish practice of allowing the insect to bite warts from the skin [139]. In Chinese medicine, chemotherapy is combined with insect therapy for non-surgical liver tumor treatment [140]. Sodium cantharidinate and vitamin B6 injections and cantharides capsules are common insect Chinese medicine [140] that contain extractions from the blister beetle (*Mylabris variabilis* Pallas) [141]. The egg cases of the praying mantis (*Mantis* Linnaeus) are used in traditional Chinese medicine to treat incontinence and frequent urination [142]. Furthermore, Chinese medicine also utilizes products derived from other animal species and herbs besides insects [140]. Another insect-inspired product described in the scientific literature is the physical-based bactericidal surface [143]. Ishwarya *et al.* [144] described the use of the seed extract of *Pedalium murex* Linn (family: Pedaliaceae) to produce silver nanoparticles. The study showed that the produced silver nanoparticles combined with Gram-positive and Gram-negative bacteria result in a larger quantity of dead bacteria than the control sample. Furthermore, experiments on mosquito larvae showed the larvicidal potential of the silver nanoparticles. Jaggessar *et al.* [143] reviewed both the natural and bio-inspired antibacterial surfaces. Nanotextured surfaces were produced inspired by the dragonfly wings, cicada wings, and butterfly wings. The surfaces produced showed varying bactericidal efficiencies [143]. Hence, additional research should investigate how to engineer a surface pattern that incorporates the best features of nano-surfaces found on insect wings. These surfaces are a helpful addition for medical implants with an associated risk of bacterial infection.

For insect-inspired medical instruments, one of the main challenges is the complexity of the insect structures found in nature. Structures such as the interlocking mechanism found in the wasp ovipositor are not possible to produce using the current microfabrication techniques [55]. This and other challenges, such as the production of biocompatible materials, might explain why many insect mechanisms are not yet applied in the development of innovative biomedical instruments. With this review, we would like to propose a new field of research called "entomomedical engineering." We define entomomedical engineering as the branch of engineering that uses insects either directly or as a source of inspiration to design and develop innovative medical strategies. The diversity of insects provides a great source of inspiration for us to evolve innovative medical treatments and instruments.

VI. CONCLUSION

This work provides an overview of the state of the art in the scientific literature describing the direct application or the bioinspiration of insects used in medical engineering. The goal was to analyze the different insects used directly or as inspiration source. This research field is what we call entomomedical engineering, i.e., an innovative branch of engineering that uses insects either directly or as a source of inspiration for innovative medical technologies. We discussed a total of 93 relevant scientific articles found in the Scopus database published over the last 20 years (2000-2020). Medical treatments directly applying insects face the challenge of social approval by both patients and clinicians. Raising awareness about insect application in medicine or extracting the insect's working principle might increase its social approval. One of the main challenges for insect-inspired medical instruments is the complexity of the insect structures found in nature. Increasing the development of microfabrication techniques might increase the clinical application of insect-inspired medical instruments. Novel medical instruments and treatments can be developed by exploring the field of entomomedical engineering.

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