

## Emerging of cardiovascular metal stent: A review on drug-eluting stent towards the utilisation of herbal coating

Siti Khadijah Lukman <sup>a</sup>, Rania Hussien Al-Ashwal <sup>a</sup>, Ahmad Zahran Md. Khudzari <sup>a, b</sup>, Syafiqah Saidin <sup>a, b, \*</sup>

<sup>a</sup> School of Biomedical Engineering & Health Sciences, Faculty of Engineering, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia.

<sup>b</sup> IJN-UTM Cardiovascular Engineering Centre, Institute of Human Centered Engineering, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia

\* Corresponding author: syafiqahsaidin@biomedical.utm.my

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### Abstract

Metal stents used in the treatment of percutaneous coronary intervention (PCI) have revolutionized in treating atherosclerosis disease. Starting from the emergence of bare metal stent (BMS), this stent has been progressively developed into drug-eluting stent (DES) and biodegradable stent. By focusing on DES, various drugs have been used to coat metal stent with the aims to overcome in-stent restenosis and stent thrombosis. Therefore, the utilisation of various drugs and polymers as coating materials was reviewed in this study to identify possible alternative to overcome the current DES problems. Even though, both complications of BMS are covered successfully by DES, however, DES projects long term complications of delayed endothelialisation, delayed wound healing and late stent thrombosis. Another alternative of herb coating on DES is considered to be a potential approach in improving endothelialisation and retarding smooth muscle cells proliferation to accelerate wound healing and to prevent late stent thrombosis.

**Keywords:** Metal stent, drug-eluting stent, drug coating, cardiovascular

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## INTRODUCTION

Cardiovascular disease (CVD) is a disease related to heart and blood vessel caused by atherosclerosis that is affecting the entire arterial circulation related to pathologic process [1]. Atherosclerosis is a build-up of plaque and fatty deposits, cellular debris and cholesterol, leads to narrowing of blood vessels [2]. This disease is the leading cause of death in the world and surpasses the number of death, caused by other diseases such as acquired immunodeficiency syndrome (AIDS) and cancer [3]. There are several risk factors that contribute to CVD such as obesity, hypertension, diabetes and smoking [1]. In, 2013, CVD has projected more than 17.3 million deaths per year and depicting 31% of all global death [4]. This statistic is presumed to increase gradually, up to more than 23.6 million by 2030 [4].

In Malaysia, CVD has led to mortality and morbidity of 36% of total deaths in 2014 [5]. Therefore, preventions must be taken aggressively and more affordable treatments should be offered to aid the increasing number of CVD cases. A coronary artery bypass graft or a less invasive technique called percutaneous coronary intervention (PCI) is a common treatment used to remove the blockage of narrowing arteries [2]. Percutaneous coronary intervention, sometimes called angioplasty is frequently performed as a treatment for atherosclerotic lesions in the coronary artery and usually involves balloon angioplasty and stent implantation [6].

Stents have been developed rapidly through many years from the evolvement of bare metal stent (BMS) to drug-eluting stent (DES) and biodegradable stent [6]. Various types of drug are used as coating materials to overcome the limitation of BMS where this type of stent

is known as DES [6]. However, DES also has long term complications such as late endothelialisation, delayed wound healing and late stent thrombosis [7]. Therefore, the aim of this paper was to provide a review on the utilisation of various drugs as coating materials in identifying possible alternative to overcome the current complications of DES. The review was divided into three sections: Stent; Commercial drug coating on DES; Herb coating on DES for cardiovascular application. In the first section, elaboration on revolution and types of stent were provided while in the second section, current commercial drugs which are being used as coating materials on DES were discussed to express the main constraint of commercial DES. In the third section, several herbs with specific therapeutic benefit, that have potential to be used in DES fabrication were presented and the final review was focused on ginseng due to its dual therapeutic functions.

### Stent

Stent is a metal wire mesh, used in PCI treatment which requires elasticity and strength to support arterial walls in reducing the chance of narrowing arteries by keeping the lumen clear from plaque development [8–10]. With diameter from 1.5 to 3.0 mm and 15 to 30 mm long [11], it is also acts as a temporary or permanent vascular scaffold, preventing restenosis and incidence of acute vessel blockage after dissection as compared with plain old balloon angioplasty (POBA) [12]. During PCI treatment, a stent is inserted along with balloon catheter to the afflicted coronary artery before it is expanding to constrict atherosclerotic plaque [13]. As the balloon catheter is inflated and withdrawn from the body, the expanded stent remains in

the artery to support the weak arterial wall. In 1964, the first angioplasty was introduced by Charles Theodore Dotter and Melvin P. Judkins [14] followed by placement of the first coronary angioplasty during a coronary artery bypass graft surgery, performed by Gruentzig and Myler in May 1977 [6]. Four months later, on 16 September 1977, Andreas Gruentzig performed the first PCI in an awake patient which has been marked as a revolution in interventional cardiology [6, 15, 16].

Coronary stent was primarily introduced in the mid-1980s [14], acts as a vascular scaffold. It has ousted the POBA as a favoured method for PCI treatment, after successful observation on

angiographic and clinical outcomes [14]. The utilisation of coronary stents is revolutionised with major refinements in stent design and composition [6]. Implantation of the first coronary BMS was performed by Jacques Puel in Toulouse [17] where restenosis rate was relatively decreased to 15-30% [3]. Coronary stent implantation was then announced as a standard procedure by National Institute for Health and Care Excellence (NICE) in the United Kingdom in May 2000 for treating patients suffering from myocardial infarction [3]. Fig. 1 illustrates the evolution of cardiovascular metal stent in treating CVD.

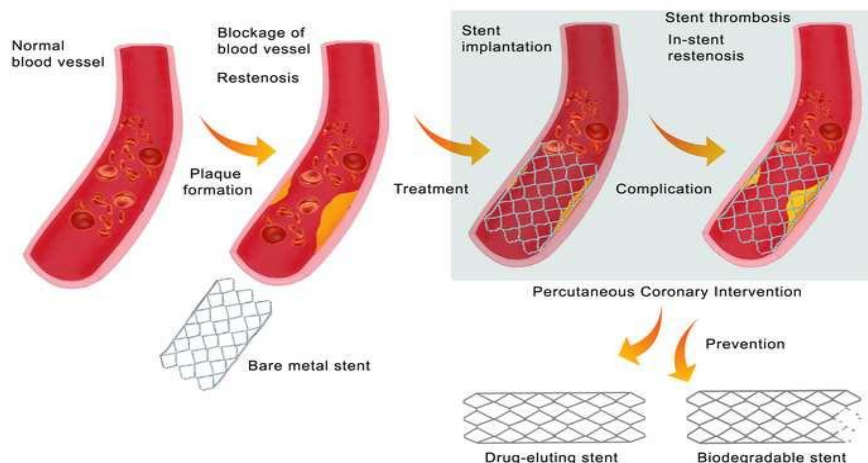


Fig. 1 Illustration of evolution of cardiovascular metal stent in treating CVD.

### Bare metal stent (BMS)

Bare metal stent is made of metallic materials such as stainless steel, cobalt-chromium, nitinol, etc, established to reduce restenosis caused by vascular recoil and to overcome complications after dissection [18]. The implantation of BMS is involving several procedures. Catheter consists of an inflatable balloon is inserted into the artery through a skin cut with a stent, fixed at the end part of the balloon [19]. A radial force exerts on the stenotic blood vessel due to dilatation of the stent. The stent stays in place and resists contraction of the blood vessel caused by permanent deformation [19].

The restenosis rate was successfully reduced by stent implantation, however, an in-stent restenosis (ISR) becomes the forthcoming problem with an occurrence of 20-35% [11, 20-21]. In a failure case, these neointima tissues that enclosed a stent once the stent is implanted into the vessel, proliferate extremely and clog the vessel that later trigger hyperplasia [19]. Besides, BMS is also regarded as a foreign material that becomes the site of origin for blood clot formation and localized inflammation [9]. A profound fibrotic response and late lumen damage are another complications of BMS where it can reduce arterial diameter by 800  $\mu$ m due to development of 400  $\mu$ m thick layer of fibrotic tissues within the stent [22].

### Drug-eluting stent (DES)

Introduction of DES is specifically to overcome the ISR. Drug-eluting stent is a drug-coated stent which functioned to accommodate drugs and to regulate drug release into surrounding tissues [8]. It has brought effectively advancement in the management of coronary vessel revascularisation. It has also deduced the occurrence of major cardiac events from 16.4% (BMS implantation) to 7.8% (DES implantation) [23]. Moreover, DES has inhibited the growth of neointimal by releasing an anti-proliferative drug locally, thus maintaining vascular patency [24]. Despite of its advantage, DES also has limitations in long-term adverse clinical events such as late thrombosis, poor vascular endothelialisation, local hypersensitivity and delayed wound healing [24].

Drug-eluting stent can be divided into three different groups based on its structure [25]: 1) Membrane covered stents, where a membrane loaded with drug is coated over a stent. The membrane controls the release of incorporated drugs into adjacent tissues and minimises loss of drug along the lumen when it is only bared to the vessel epithelium.

However, due to limited anchoring strength at the site of implantation, the membrane-covered stent has higher rate of movement in the blood vessel. Besides, mechanical properties of the stents are still diminished, in longitudinal direction including its flexibility, extension capability and collapse pressure.

2) Drug-reservoirs based stents, where drugs or drug/polymer mixture are filled in different shapes of drug reservoirs that are formed within the stent struts. The main advantage of this type of DES, is the ability to control drug distribution at implantation site by changing reservoir design and quantity of drug inside the reservoir. However, intricate approaches are needed to form reservoirs within the tiny structure of stent struts and to incorporate drug into the reservoirs. 3) Layer-coated stents, where stent struts are coated with a thin layer of drug integrated carrier. This type of DES has exceptional mechanical properties compared to the membrane-covered stents. However, the drug is washed away from the action site when this monolithic coating layer is exposed to blood stream through the lumen.

All these scenario lead to the development of DES with an intention to restrain ISR and neointimal proliferation [26]. Besides, requirement for repetition of interventions is reduced and the coronary arteries also remain open for lengthy time after the implantation of DES [13]. Although DES showed exceptional performance, however, late thrombosis and restenosis are still arisen following DES implantation [27, 28]. These problems are possibly caused by long haul impact of polymer, holding the stent while delivering drug into the arterial wall [26]. Another factor is lies on the inability of endothelialisation around the vessel wall [2].

### Biodegradable stent

Until the vessel remodels and heals, a biodegradable stent is projected to open narrowed blood vessel temporarily before degraded progressively [29]. Biodegradable stent is forecasting to restore blood flow and to provide mechanical support temporarily to prevent vessel recoil [30, 31]. Besides, it needs to possess certain point of fracture toughness and sustained deformations in avoiding broken struts or fragmentation following implantation [31, 32]. The materials must be able to degrade following gradual resorption that match with the healing period of blood vessel where inflammatory responses and tissue overload should not be provoked by the degradation release

[31]. Great biocompatibility, good fatigue and physical resistance to aging, ability to withstand high-temperature heat processing, high-energy laser cutting and critical sterilisation conditions are other necessary features required by the materials [31].

Bioactive stents like DES are notably known for its great achievement in curing patients with coronary artery disease. However, they still have flaws in long-term reperfusion [13]. Therefore, clinicians mostly believe that stent is required to reinforce mechanical structure of vessel wall transiently during the remedial period as the healing of the artery is between 3 and 6 months following stent implantation [13]. The possibility of late complications such as restenosis and thrombosis due to the placement of permanent device can be avoided with utilisation of temporary device that degrades after certain period [13].

Biodegradable implant offers more than permanent metallic implants in terms of physiological reconstruction, reconstitution of local vascular compliance, and a brief, limited, longitudinal, and radial straightening effects including the probability of growth [33]. Materials used in the development of biodegradable stents are polymers and metals: either magnesium or iron-based [29, 34]. Biodegradable polymers have promising properties to serve as a biodegradable implants, however severe inflammation is recorded following implantation due to their degradation products. Its slow expansion in blood could cause injuries to the blood vessel [35]. As for magnesium alloy, it has high mechanical properties compared to polymer but it dissolves too fast to match the clinical requirements of cardiovascular application [35].

#### Commercial drug coating on drug-eluting stent

There are several drugs have been incorporated within polymers as a coating material on DES. Two types of commercialised drugs commonly used to coat stents are "limus" family and cancer chemotherapy drug paclitaxel [22].

The first generation of DES using sirolimus and paclitaxel hinder restenosis by suppressing production of smooth muscle cell, however, late stent thrombosis is still occur following the implantation [11]. The second generation of DES is the utilisation of sirolimus derivatives including everolimus, zotarolimus and biolimus [36–38, 11]. They revamped clinical results of repeat revascularisation, myocardial infarction and stent thrombosis [39, 40]. However, burst release of drugs bombarding the occurrence of thrombosis despite of their advantages.

Sirolimus or also known as Rapamycin is a novel immunosuppressive agent that can interrupt the pathway of vascular endothelium growth factor (VEGF) and limiting tumor production to avoid angiogenesis [41]. It has been approved by Food and Drug Administration (FDA) as a primary immunosuppressant due to its antiproliferative property and its strong anti-rejection effects that

reduces cardiac allograft vasculopathy and absence of toxicity in the kidneys in cardiac transplant patients [42]. A comparison by Park *et al.* [43] showed that cell viability of rabbit iliac artery on tacrolimus-eluting stent with biodegradable polymer, sirolimus-eluting stent and everolimus-eluting stent were reduced in a dose-dependent manner where all drugs inhibited smooth muscle cell proliferation. However, the growth of endothelial cells was retarded in the treatment with the tacrolimus compared to the sirolimus and everolimus [43]. Significant different in fibrin score was also reported where the tacrolimus group demonstrated better score than the sirolimus and everolimus [43].

Yazdani *et al.* [44] evaluated coating integrity as a function of time in their *in vivo* studies by comparing several commercial available DES: Xience prime everolimus-eluting stent, Resolute zotarolimus-eluting Stent, Taxus paclitaxel-eluting stent and Nobori biolimus A9-eluting stent. The everolimus and zotarolimus types of DES have less coating deformity than the paclitaxel and biolimus A9 where coating defect was not observed on most struts [44]. Only a few struts of the everolimus type of DES showed minor defects and for the zotarolimus type of DES, the struts showed no coating defects at all time points except at 180 days [44]. However, webbing and uneven coating were noticed on the paclitaxel struts while polymer cracking appeared on majority of the biolimus A9 struts [44].

In a work by Stone *et al.* [45], a comparison was done on patients with ST-segment elevation, suffered from myocardial infarction where the disease was treated with paclitaxel-eluting stents and BMS. Through international, prospective and controlled trials, the rate of angiographic restenosis was significantly decreased [45]. The rate of recurrent ischemia required repeat revascularisation method in paclitaxel-eluting stent treatment was also decreased, compared with the patients who received BMS within the first year [45]. On the other work by Jazi *et al.* [46], they investigated the effects of implantation of BMS and DES on circulating endothelial cells. The studies were performed in 22 patients suffered from PCI where the amount of cell which acted as cellular markers of endothelial dysfunction following PCI was determined, before and after a week of stent implantation [46]. The circulating endothelial cells count in the DES group was significantly lower compared to the BMS group after one week of stent implantation. This finding demonstrated lower endothelial injury after the DES implantation.

Table 1 summarise the previous studies on commercial drug coating for DES fabrication which consists of everolimus, zotarolimus, paclitaxel, biolimus, sirolimus and tacrolimus. From these review, the main constraint of the commercial DES is lying on the post-implantation scenario of lack endothelialisation and delayed wound healing. Therefore, a review on the utilisation of herb as coating materials was done due to its promising values in promoting proliferation of endothelial cells and inhibiting differentiation of smooth muscle cells to prevent late stent thrombosis.

**Table 1** Summary of previous studies on commercial drug coating for DES fabrication.

Authors, Year	DES	Drug category	Review Summary	Reference
Yazdani <i>et al.</i> , 2016	Xience prime everolimus-eluting stent, Resolute zotarolimus-eluting stent, Taxus paclitaxel-eluting stent and Nobori biolimus A9-eluting stent	Everolimus, zotarolimus, paclitaxel and biolimus A9	Less coating deformity on everolimus and zotarolimus type of DES. Minor defects on a few struts of everolimus type of DES and no coating defect on zotarolimus type of DES at all time points except at 180 days of analysis. Webbing and uneven coating on paclitaxel struts and polymer cracking on majority of biolimus A9 struts.	[44]
Park <i>et al.</i> , 2015	Tacrolimus-eluting stent, sirolimus-eluting stent and everolimus-eluting stent	Tacrolimus, sirolimus and everolimus	Decrement viability of smooth muscle cells in rabbit iliac artery for all groups in dose-dependent manner. Growth retardation of endothelial cells and higher fibrin score on tacrolimus group compared to sirolimus and everolimus groups.	[43]
Jazi <i>et al.</i> , 2011	Sirolimus-eluting stent (Cypher) and paclitaxel-eluting stent (Taxus)	Sirolimus and paclitaxel	Lower count of endothelial cells on sirolimus and paclitaxel groups compared to BMS or non-coating stent after one week of implantation	[46]
Stone <i>et al.</i> , 2009	Paclitaxel-eluting stent	Paclitaxel	Lower rate of angiographic restenosis and lower rate of recurrent ischemia on paclitaxel group compared to BMS or non-coating stent.	[45]

### Herb coating on des for cardiovascular application

Several herbs (Fig. 2) have been incorporated within polymers for the purpose of stent coating. For example, a purified compound of Chinese herb medicine, *Tripterygium wilfordii* or known as Triptolide has shown anti-proliferative effect through *in vivo* and *in vitro* analyses. It has an ability to suppress the proliferation of vascular smooth muscle cells, inactivates the pathway of mitogen-activated protein kinase (MAPK), modulates the protein cycle of p21cip1 cell and reduces the phosphorylation of retinoblasma protein [47]. The triptolide-coated stent also displayed attenuation of neointimal formation compared to the BMS after one month of implantation [47]. In a study by Lee *et al.* [48], they mixed water extractions derived from eight herbal plants of *Pinellia ternate* Ten. Ex Breitenb., *Atractylodes macrocephala* Koidz., *Gastrodia elata* Blume, *Citrus unshiu* Marcow., *Poria cocos* Wolf, *Crataegus pinnatifida* Bunge var. *typica* C. K. Schneider, *Siegesbeckia pubescens* Makino. and *Coptidis japonica* Makino to be coated on stent. They notably found reduction in restenosis, retardation of neointimal hyperplasia and inhibition of

smooth muscle cell growth [48]. However, high dose of these herbal plants has slightly increased the toxicity of the samples in their animal study [48].

Karki *et al.* [49] administrated ethanolic extract of Magnolia Cortex (MOE) orally on intimal tissues in rat carotid artery caused by balloon endothelial denudation. They expressed that the MOE extract which was originated from Magnoliaceae has therapeutic potential in the setting of vascular injury as they successfully inhibited the migration of smooth muscle cell and suppressed intimal thickening in rat carotid artery. In another study, Zulaika *et al.* [50] worked on the development of poly(lactic-co-glycolic acid) (PLGA) and ginsenoside coating on stainless steel 316L (SS316L) substrates using a dip coating technique as a possible alternative to solve the current problems of late restenosis and poor endotheliasation. However, further investigation on the ability of the PLGA/ginseng coated stent should be carried out as they are presumed can retard the growth of smooth muscle cells and promote the proliferation of endothelial cells. Table 2 summarise the previous findings on herbs coating on DES.

**Table 2** Summary of previous studies on herb coating which possibly be used for DES fabrication.

Authors, Year	Herbs Coating	Review Summary	Referen ce
Tao <i>et al.</i> , 2011	Triptolide ( <i>Tripterygium wilfordii</i> )	Suppress proliferation of vascular smooth muscle cells, inactivate mitogen-activated protein kinase (MAPK) pathway, modulate protein cycle of p21cip1 cell and reduce phosphorylation of retinoblasma protein and attenuate neointimal formation compared to BMS or non-coated stent after one month of implantation.	[47]
Lee <i>et al.</i> , 2011	Water extractions of eight herbal plants ( <i>Pinellia ternate</i> Ten. Ex Breitenb., <i>Atractylodes macrocephala</i> Koidz., <i>Gastrodia elata</i> Blume, <i>Citrus unshiu</i> Marcow., <i>Poria cocos</i> Wolf, <i>Crataegus pinnatifida</i> Bunge var. <i>typica</i> C. K. Schneider, <i>Siegesbeckia pubescens</i> Makino., and <i>Coptidis japonica</i> Makino)	Reduce restenosis, retard neointimal hyperplasia and inhibit smooth muscle cell growth. Increase toxicity at high dose of water extractions.	[48]
Karki <i>et al.</i> , 2012	Ethanolic extract of Magnolia Cortex (MOE)	Inhibit migration of smooth muscle cells and suppress intimal thickening in rat carotid artery.	[49]



**Fig. 2** Potential herbs that can be used for DES coating.

### Ginseng in cardiovascular application

Ginseng is one of the herb plants that has been used as an alternative remedy since years ago by the people in Eastern Asia Countries [51]. People believes that ginseng can cure illness and

relieves stressful lifestyle [52]. Panax ginseng is belonged to ivy family of Araliaceae [53] and it is widely used in Asian countries to keep the body homeostasis constant and strengthen the vital energy [54]. Panax ginseng can be divided into two types which are red



ginseng and white ginseng. Ginsenosides are the main active ingredients inside the ginseng, accounted at least 30 different ginsenosides, extracted from the roots, stems or leaves of Panax ginseng [55]. It has been reported that ginsenosides confer many positive impacts to cardiovascular system [56–59]. Based on the structure of aglycon with a dammarane skeleton, ginsenosides can be divided into three different categories which are protopanaxadiol (PPD), protopanaxatriol (PPT) and oleanane saponins [60]. The PPD- and PPT- type ginsenosides are further classified into several subgroups based on the position and number of sugar moieties attached to the aglycon at positions C3 or C6 and C20 [60]. Qin *et al.* [55] reported that the administration of total ginsenosides has suppressed monocrotaline (MCT)-induced pulmonary hypertension, an established model similar to human pulmonary hypertension. Total ginsenosides has significantly decreased full term right ventricular systolic pressure, right ventricular hypertrophy index and lung weight/body weight in the MCT-induced pulmonary hypertension, indicating protective impact on pulmonary hypertension given by the total ginsenosides where these results were obtained from the assessment of right ventricular systolic pressure and right ventricular hypertrophy index.

Furthermore, Zu *et al.* [61] verified the protective effect of Rg1 ginsenoside on intestinal ischemia/reperfusion or hypoxia/reoxygenation by activating the pathway of Wnt/  $\beta$ -catenin, suppressing apoptosis and inhibiting the production of reactive oxygen species [61]. The effect of Korean Red Ginseng extract (KRGE) also has been tested on apoptosis of human umbilical vein endothelial cells (HUVECs) in a serum-deprived apoptosis model [62]. The KRGE inhibited serum deprivation-induced apoptotic cell death in the HUVECs and displayed protective effect higher than the American Ginseng extract (AGE). The KRGE also has an anti-apoptotic property to prevent endothelial cell death [62]. Interestingly, it has an ability to retard tumor cells when tested on anticancer drug cisplatin-induced HeLa cells [62]. Ginsenoside Rc is one of the compositions in Panax ginseng that exhibit anti-cancer, anti-inflammatory, anti-obesity and anti-diabetic effects. As shown in a flow cytometric analysis, ginsenoside Rc mediates strong anti-inflammatory activity by blocking Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) expression in synovial cells, where TNF- $\alpha$  is a pro-inflammatory cytokine that develops rheumatoid arthritis [63].

### Ginseng coating on drug-eluting stent

Anti-proliferative and anti-thrombotic properties are among crucial characteristics required for the development of DES. Both properties demonstrate the ability of DES to inhibit the proliferation of vascular smooth muscle cells and to promote the proliferation of endothelial cells specifically to overcome recent problems of DES such as poor endothelialisation, ISR and late thrombosis. In our previous research, we have successfully incorporated ginsenosides Rg1 and Re with PLGA as a coating material on metallic stent using a dip coating technique [49]. However, the theory to retard the proliferation of vascular smooth muscle cells and to induce the growth of endothelial cells are remain unknown for ginseng coated stent. Further analyses are needed to investigate the potential of this stent to express their function as DES. Several other techniques also should be explored to develop a stable herbal based drug-eluting coating on metallic stent that possess optimum characters to function as DES.

### CONCLUSION

Stent used in PCI has revolutionized over years in the treatment of atherosclerosis, starting from BMS, DES and biodegradable stent. Various drugs such as sirolimus, its derivatives and paclitaxel have been used as coating materials on DES to overcome restenosis and stent thrombosis. However, long term complications of delayed endothelialisation, delayed wound healing and late stent thrombosis become an obstacle in the implantation of DES. Therefore, providing a new strategy is an attempt to combat these problems. The utilisation of herbs as coating materials should be considered to be a possible way to reduce the current DES complications.

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