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REVIEW

The latest trends in the design of electrochemical biosensors for the diagnosis and monitoring of diabetes mellitus

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ABSTRACT

AIMS: This review article focuses on electrochemical biosensors in the diagnosis of diabetes mellitus and their latest trends and advances. In particular, non-enzymatic, non-invasive, wearable, and non-glucose biosensors are described.

METHODS: The current literature was searched and recent works on this matter were cited and discussed in the text of this paper.

RESULTS: The overworld health problem, the incurable disease, the global burden on health insurers and society, and above all one of the leading causes of death – all characterize diabetes mellitus, a lifelong chronic disease that affects hundreds of millions of people around the world. The new types of biosensors bring new opportunities in the care of diabetic patients and improve current methods. The practical relevance of the recent findings is expected in medicine in next years.

CONCLUSIONS: The authors summarized the modern possibilities of biosensing, their pros and cons, and their perspectives for the future. The discussion outcome from the current literature *(Tab. 4, Fig. 1, Ref. 63)*. Text in PDF *www.elis.sk*

KEY WORDS**:** diabetes mellitus, electrochemical biosensors, non-enzymatic glucose sensors, non-invasive glucose sensors, wearable glucose sensors, glycated haemoglobin glucose sensors, glycated albumin glucose sensors, insulin glucose sensors.

Introduction

Diabetes mellitus (DM) is a term used to describe a group of metabolic disorders characterized by elevated blood glucose levels – hyperglycemia. Hyperglycemia is caused by an absolute insulin deficiency or insulin resistance in tissues (1, 2). DM as a chronic disease is a global health problem with a significant impact on human life and the health care system. The current socioeconomic status rapidly increases the development of DM in many parts of the world (3, 4). According to the National Diabetes Statistic Report (2020), 10.5 % of Americans suffer from diabetes and almost 3 % of Americans have undiagnosed hyperglycemia in all age categories. That is more than 40 million diabetic patients just in the United States (5). The most common form, type 2 diabetes, has affected more than 460 million people worldwide in 2017 and its number is growing rapidly (4).

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The most common forms of DM are type 1 diabetes, type 2 diabetes, and gestational diabetes, but DM can also be caused by exocrine pancreatic diseases, endocrinopathies, drugs, genetic defects, etc. (1, 2). Type 1 DM is known as immune-mediated diabetes. Pancreatic β-cells are destroyed by the patient's immune system, leading to an absolute insulin deficiency, which makes it classified as an autoimmune disease. Only 5–10 % of the patients with DM suffer from type 1, formerly known as juvenile DM, due to its onset at an early age. Type 2 DM develops over the years from a relative insulin deficiency to both defects of secretion and action of insulin. An unhealthy lifestyle with a poor diet, insufficient physical activity, obesity, and high blood pressure is the biggest risk factor for the development of type 2 DM. Gestational diabetes is diagnosed for the first time during pregnancy, but hyperglycemia can persist even after delivery (1, 6). Undiagnosed and untreated DM leads to several health disorders, including cardiovascular diseases, diabetic nephropathy, neuropathy, and retinopathy, and these comorbidities decrease the quality of life and lead to premature morbidity (4,7).

An essential part of an early and correct diagnosis is a precise diagnostic method, where the blood glucose level is the key parameter. A biosensor is an analytical device, in which an immobilized biological component (enzyme, antibody, antigen, DNA, whole cells, and tissues) interacts with the analyte to produce a measurable signal. An electrochemical biosensor is a type of biosensor, where the biochemical reaction creates an electrical sig-

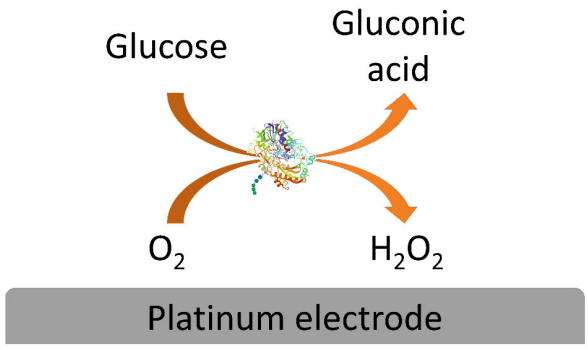

Fig. 1. Scheme of the first electrode for glucose measurement.

nal, electrons are generated or used, and the flow rate of electrons is proportional to the concentration of the analyte. The popularity of electrochemical biosensors has grown over the years in many industrial, environmental, and medical fields due to their high sensitivity and specificity, simple construction, easy handling, portability, and low cost (8–11). Electrochemical biosensors are currently among the most widely used methods of diagnostics of DM. Its history dates to the 1960s, when Clark and Lyons designed the first enzyme-based glucose sensor. The construction was based on an oxygen electrode with trapped glucose oxidase in a semipermeable dialysis membrane on its surface, and a drop of oxygen was measured with a platinum electrode. The chemical process that takes place on the electrode is shown in Figure 1 (7, 12, 13).

Since the first design of the glucose biosensor, biosensors for the diagnosis of DM have made tremendous progress, glucose non-enzymatic and wearable biosensors have been introduced, blood is not the only biological material suitable for analysis, DM can be diagnosed and monitored by analysis of insulin and hemoglobin levels, and point-of-care testing devices have been implemented to practice. The current trend in the diagnosis and monitoring of DM is presented in the following chapters.

Glucose biosensors

DM, as the seventh leading cause of death with 5 % of the affected population, is a worldwide problem. Monitoring glucose levels in diabetic patients is a crucial parameter for the diagnosis and monitoring of DM (9). Although biosensors aimed at measuring analytes other than glucose have been recently researched, glucose biosensors are still the most common tool in the diagnosis of DM and this chapter is focused on them.

Non-enzymatic glucose sensors

Although the performance of enzymatic glucose biosensors has been significantly improved due to their three-generation development, the effort to design non pH and temperature-dependent biosensors that do not succumb to loss of enzymatic activity in the extreme environment has increased. Nanomaterials, generally materials smaller than 100 nm in size, their synthesis, molecular design, function, and character have been studied in the last few decades, and in particular, metals, metal alloys, metal hydrates, metal sulfides, metal nitrides, and metal oxides have been extensively studied for their use in nonenzymatic glucose biosensors. These materials have shown the ability to oxidize glucose in both neutral and alkaline environments and, due to their porous surface with high accessibilities, low density, high surface area, different chemical compositions, and interlinked hierarchical porosity at various lengths, enable excellent ion and electron transfer, especially metal oxides, which have been shown to be highly stable, easily accessible, and biocompatible (14, 15).

Metal oxide nanomaterials have been used in the work of Haghparas and co-authors (2021), Vinoth and co-authors (2021), and Hovancova and co-authors (2020). The first-mentioned work was focused on the design of dumbbell-shaped double shelled hollow nanoporous CuO/ZnO microstructures by the hydrothermal method using pluronic F-127 as a surfactant (16). Zinc oxide quantum dots immobilized on multiwall carbon nanotubes were used as a sensing material in a Vinoth and co-authors glucose sensor (2021). Hovancova and co-authors (2020) designed a glucose sensor based on a titanium metal covered with detection by titanium dioxide with electrochemical impedance spectroscopy (16–18).

Metals, namely copper, were used in the form of nanospheres as sensing material in the work of Yu and co-authors (2021). The nanospheres were prepared by irradiating Cu_2O microparticles in ethanol with a 1064 nm laser. Copper nanoparticles anchored to lased-induced graphene electrodes were also used in the construction of glucose non-enzymatic sensors by Zhang and co-authors (2020) (19, 20).

Tab. 1. Analytical characteristics of non-enzymatic glucose sensors.

Nanomaterial	LOD (nM)	Linear range (μM)	Detection	Reference
Nanoporous CuO/ZnO microstructures	358	0.500–100 10^3	CA	(16)
ZnO QDs on MWCNTs	208	0.100–2.50	CA	(18)
Ti covered with TiO_2	1.20 10^6	1.00 10^3–15.0 10^3	EIS	(17)
Cu NSPs	–	–	CV	(19)
Cu NPs			CA	(20)
Cu_2ZnSnS_4 QDs	13.4	0.500–2.00 10^3	CA	(22)
$CoTe_2$ NSs	590	10.0–250	CA	(21)
$Cu(OH)_2$ NTs	350	1–1.78 10^3 and 1.78 10^3–6.53 10^3	CA	(23)
Ni-Co-Fe hydroxide NSPs	98.0	0.250–1.00 10^3 and 1.00 10^3–5.00 10^3	CA	(24)

LOD – limit of detection, CA – chronoamperometry, QDs – quantum dots, MWCNTs – multiwall carbon nanotubes, EIS – electrochemical impedance spectroscopy, NSPs – nanospheres, CV – cyclic voltammetry, NPs – nanoparticles, NSs – nanosheets, NTs – nanotubes

Quantum dots on Nafion binder and fluorine-doped tin oxide glass as supporting substrates were fabricated as nonenzymatic glucose oxidizing catalysts in the work of Zhou and co-authors (2021). Farid and co-workers (2021) prepared porous cobalt telluride nanosheets as an active catalyst for glucose detection (21, 22).

Copper(II) hydroxide nanotubes prepared by electrodeposition of Cu clusters on a thin film of electropolymerized polypyrrole were used to manufacture an amperometric glucose sensor by Manafi-Yeldaghermani and co-authors (2021) (23). Amorphous Ni-Co-Fe hydroxide nanospheres with a homogeneous distribution of metals are fabricated directly on a graphite substrate by an electrodeposition method in the work of Li and Zhao (2019) (24).

Analytical characteristics of the described sensors are summarized in Table 1.

Although metal oxides were mentioned as the most promising sensing materials in the construction of nonenzymatic glucose sensors, the limits of detection summarized in Table 1 showed the worst sensitivity of sensors based on metal oxides. On the other hand, all detection limits are sufficient for the analysis of glucose from blood samples, the most widely used biological material in practice, so extremely low detection limits are not required. However, as we describe in the following chapters, tests for the analysis of glycemia from other biological materials have recently been investigated. It is worth mentioning that despite higher detection limits, non-enzymatic glucose biosensors based on metal oxides are currently the most studied. In the last three years, nonenzymatic glucose sensor based on metal-oxides nanomaterials were also designed by Awais and co-authors (2021), Babulal and co-authors (2021), Lotfi and co-authors (2021), Yang and co-authors (2021), Yin and co-authors (2021), Espro and co-authors (2020), Wei and co-authors (2020), Jo and co-authors (2020), Inyang and co-authors (2020), Lin and co-authors (2019) and many others (25–34).

Non-invasive and portable glucose biosensors

The name non-invasive means without harm and painlessly, in practice it means that there is no injury to blood vessels or damage to the skin during sampling. Although blood is the most studied bodily fluid for measuring glucose. Glucometers, devices used in practice, rely on blood sampling, the risk of infection and pain is a major problem. And the benefit of non-invasive glucose determination is just the prevention of potential infection and patient trauma (9, 35). Non-invasive glucose sensors are not in contact with blood; other body fluids including sweat, tears, and saliva are used for the analysis of glucose levels. These sensors seem to be excellent candidates for the treatment of DM, but, because glucose levels in sweat, tears, and saliva are lower than in blood, these sensors must be much more sensitive (13). For example, the reported glucose level in sweat is between 0.06 and 1 mM (36). In the management of DM, continuous monitoring of glucose levels is necessary, especially during physical activity. Thus, wearable non-invasive glucose sensors seem to be the future of DM management. On the other hand, the main problem with this kind of device is the challenge of reproducible sample collection (13, 35).

To avoid this problem and to invent a non-invasive or non-invasive wearable glucose sensor that can be implemented in practice, many studies and research have been done recently.

Sensors based on saliva analysis were invented, for example, by Adeniyi and co-authors (2021), Chakraborty and co-authors (2019), and Coyle and co-authors (2019). The first-mentioned work is a non-enzymatic electrochemical sensor based on a glassy carbon electrode modified by a single-walled carbon nanotube/reduced graphene oxide/cobalt phthalocyanines nanohybrid (37). Chakraborty and co-authors invented a non-enzymatic glucose sensor based on a working electrode consisting of Au nanoparticles decorating CuO nanorods (38). Coyle and co-authors (39) designed Au honeycomb modified with Co_3O_4 needles as a non-invasive electrochemical sensor was designed by Coyle and co-authors (39).

The non-enzymatic glucose sensor for tear analysis was fabricated by Romeo and co-authors (2018) and was based on inkjet printing electrodes on a flexible polyethylene terephthalate substrate modified by CuO microparticles (40).

Sweat glucose analysis is probably the most interesting non-invasive method, as it is the base of wearable glucose sensors intended for continuous glucose level monitoring. Alam and Howlader (2021) invented a non-enzymatic glucose sensor based on native copper oxide on copper foil (41). A glucose sensor based on a glassy carbon electrode with low-density polyethylene and covalently immobilized glucose oxidase was designed for the analysis of sweat glucose by Fabregat and co-authors (2021) (42). Zhao and co-authors (2019) invented a wearable non-invasive electrochemical sensor for a glucose sweat analysis based on a highly stretchable and conductive gold fiber with Prussian blue and immobilized enzyme glucose oxidase (43).

Analytical characteristics of the described sensors are summarized in Table 2.

Tab. 2. Overview of non-invasive and wearable sensors.

Sensor	LOD (μM)	Linear range (μM)	Detection	Biological material	Reference
GCE-SWCNT/rGO/CoPc	0.120	0.300–500 and 500–5 10^3	CA	Saliva	(37)
Au NPs decorated CuO NRs	0.170	5.00–1.33 10^3	CV, CA	Saliva	(38)
Au honeycomb modified with Co_3O_4 needles	20.0	20.0–1.00 10^3	CV, CA	Saliva	(39)
Inkjet printing electrodes	2.99	3.00–700	CV, CA	Tears	(40)
CuNOx on Cu foil	94.2	50.0–7.00 10^3	CV	Sweat	(41)
GCE with deposited PT-LDPE and covalently immobilized GOx	<50.0	50.0–1.00 10^3	CA	Sweat	(42)
GF with PB and GOx	6.00	0–500	CA	Sweat	(43)

LOD – limit of detection, GCE-SWCNT/rGO/CoPc – glassy carbon electrode modified by single-walled carbon nanotube/reduced graphene oxide/cobalt phthalocyanines, CA – chronoamperometry, NPs – nanoparticles, NRs – nanorods, CV – cyclic voltammetry, CuNOx – copper native oxide, GCE – glassy carbon electrode, PT-LDPE – plasma-treated low-density polyethylene, GOx – glucose oxidase, GF – gold fiber, PB – Prussian blue

Tab. 3. Overview of sensors for glycated hemoglobin a glycated albumin detection.

Sensor	Analyte	LOD (μM)	Linear range (μM)	Detection	Reference
rGO-MWCNTs-Pt NPs composite on Au electrode with FAOx	GHb	$100\ 10^{-3}$	$0.050–1.00\ 10^{3}$	CV	(48)
r-GO-Au nanocomposite with a thiolated DNA aptamer	GHb	$1\ 10^{-3}$	$1.00\ 10^{-3}–13.8$	DPV	(49)
FTO electrode with CHIT, GO, An NPs and FPOx	GHb	$300\ 10^{-3}$	$100–2.00\ 10^{3}$	CV, DPV	(50)
SPE with aptamers modified by the sulfhydryl and ferrocene group	GHb	$4.67\ 10^{-6}$	$5.56\ 10^{-3}–0.778$	DPV	(51)
GCE with rGO, Au NPs, and anti-GA aptamers	GA	$1.05\ 10^{-3}$	$3.00\ 10^{-2}–1.50\ 10^{-1}$	SWV	(52)
SPE with FAOx and	GA	–	0–500	CA	(53)
SPCE with GO and aptamer	GA	$0.130\ 10^{-3}$	$0.150\ 10^{-3}–0.750$	SWV	(54)

LOD – limit of detection, rGO – reduced graphene oxide, MWCNT – multiwall carbon nanotubes, NPs – nanoparticles, FAOx – fructosyl amino oxidase, GHb – glycated hemoglobin, CV – cyclic voltammetry, DPV – differential pulse voltammetry, FTO – fluorine tin oxide, CHIT – chitosan, GO – graphene oxide, FPOx – fructosyl peptide oxidase, SPE – screen-printed electrode, GCE – glassy carbon electrode, HARC – hexaammineruthenium(III) chloride, CA – chronoamperometry, SPCE – screen-printed carbon electrode

However, the invention of the wearable sensor is still a tricky matter as the sensor must be sufficiently sensitive and, in addition, sampling, impact resistance, and water resistance must be ensured. Colorimetric glucose sensors also seem to be very suitable at this point, because the colorimetric reaction is much easier to detect than the electrochemical reaction, as described by Xiao and co-authors (2019), which is based on microfluidic thread/paper-based and smartphone camera detection (44).

Glycated hemoglobin and albumin biosensors

Over the years, the glucose level has been the main and only measured parameter for the diagnosis and monitoring of DM. On the other hand, the blood glucose level shows the patient´s condition at the time of sampling, but does not correspond with his long-term state (35). Glycated hemoglobin, also known as HbA1c, is a form of hemoglobin created by the reaction of hemoglobin with elevated blood glucose levels by non-enzymatic glycation (45, 46). According to the American Diabetes Association, the International Diabetes Federation and the World Health Organization, the diagnosis of DM is possible by an oral glucose tolerance test or by measuring HbA1c. Currently, HbA1c has also become an important biomarker for long-term diabetes monitoring, as it reflects glucose blood levels within 2–3 months. On the other hand, blood levels of HbA1c can be affected by many diseases and conditions that influence the lifespan of a red blood cell, for example, HbA1c decreases after a recent transfusion, blood loss, or anemia and increases during asplenia or iron-deficiency anemia (45, 47). The same glycation mechanism that acts on hemoglobin acts on other blood proteins, the most relevant of which is albumin (46). Although glycated albumin (GA) reflects only a 2–3 weeks period of blood glucose levels, GA levels are not affected by the lifespan of red blood cells, so it can be as good a biomarker as HbA1c, which may be even better (47).

The nanomaterial composite consisting of 3D-structured reduced graphene oxide, multiwalled carbon nanotubes, and platinum nanoparticles was deposited on the surface of a working gold electrode together with fructosyl-amino oxidase enzyme as a sensing platform for the detection of HbA1c in the work of Jain and co-authors (2017) (48). Jaberi and co-authors (2019) intended to develop a portable and precise, but inexpensive, sensor for HbA1c detection. Their nano biosensor was based on reduced graphene oxide and gold with a hierarchical architecture electrodeposited on a graphite sheet electrode and thiolated DNA aptamer as a bioreceptor (49). The detection of HbA1c based on the determination of its proteolytic digestion product, fructosyl valyl histidine, has been described in the work of Shahbazmohammadi and co-authors (2020). The sensor consists of fructosyl peptide oxidase immobilized on the electrode surface modified by chitosan, graphene oxide, and gold nanoparticles (50). The aptasensor for the rapid and selective electrochemical detection of HbA1c was designed by Feng et al (2021). Screen-printed electrodes with aptamers that specifically binding HbA1c were modified by the sulfhydryl and ferrocene group at the 3 and 5´-end of aptamers in this work (51).

A glassy carbon electrode modified with reduced graphene oxide, gold nanoparticles, and anti-GA aptamer was used as a sensor for the determination of GA in the work of Farzadfard and co-authors (2020) (52). Another electrochemical sensing system for the determination of GA was introduced in the work of Hatada and co-authors (2017), where a screen printed carbon electrode was made with the enzyme fructosyl amino acid oxidase deposited and chloride as the electron mediator (53). Free graphene oxide in solution with modified G8 aptamer was used as a sensing complex on the surface of the screen-printed carbon electrode for the determination of GA in the work of Waiwinya and co-workers (54).

The analytical characteristics of the described sensors are summarized in Table 3.

HbA1c together with GA may serve as an important marker of prediabetes. GA levels are not affected by anemia, so it is a useful marker in anemic and pregnant patients and also to determine the most effective treatment; on the other hand, HbA1c is important in evaluating the long-term condition of patients (45). Both GA and HbA1c provide a more reliable view of the diagnosis and treatment of DM. Integrating GA and HbA1c assays into clinical practice together with the development of point of care testing devices is the future of diagnosis and treatment of diabetes mellitus (46).

Insulin biosensors

Insulin is an endocrine peptide hormone secreted by the pancreas that is responsible for regulating carbohydrate metabolism and balancing blood glucose levels in humans and animals. In particular, it binds to the receptors bound to the plasma membrane in target cells and provides glucose entry into cells. Disruption of

Tab. 4. Overview of sensors for insulin detection

Sensor	LOD (μM)	Linear range (μM)	Detection	Reference
LSGE with aptamer and probe	$22.7\ 10^{-9}$	$0.100\ 10^{-6}$ – 1.00	DPV	(57)
SPCE with CHIT-MWCNTs-Cu NPs	1.11	0.100–4.00	CV	(58)
SPCE with CHIT-MWCNTs-Co NPs	$25.0\ 10^{-3}$	0.050–5.00	CV	(58)
SPCE with MWCNTs and QDs	$0.100\ 10^{-3}$	$0.100\ 10^{-3}$–$5.00\ 10^{-3}$	SWV	(59)
MIP with $K_3[Fe(CN)_6]$/ $K_4[Fe(CN)_6]$ probe	$7.24\ 10^{-9}$	$1.00\ 10^{-8}$–$5.00\ 10^{-7}$	DPV	(60)
Anti-insulin fragment scFv and ferricyanide probe	$10.0\ 10^{-6}$	$10.0\ 10^{-6}$– .100	EIS	(61)

LOD – limit of detection, LSGE – laser-scribed graphene electrode, DPV – differential pulse voltammetry, SPCE – screen-printed carbon electrode, CHIT – chitosan, MWCNTs – multi-walled carbon nanotubes, NPs – nanoparticles, CV – cyclic voltammetry, QDs – quantum dots, SWV – square wave voltammetry, MIP – molecularly imprinted polymer, EIS – electrochemical impedance spectroscopy

insulin metabolism leads to failure of the homeostasis of glucose and DM and associated complications (55, 56). Therefore, insulin, together with glucose, is the main biomarker for monitoring and control of DM (3). Countless insulin sensors with different structures and mechanisms of action have been developed, and we describe some of the newest ones below.

An electrochemical aptasensor based on laser-scribed graphene electrodes was invented by Liu and co-authors (2022). The sensor concept is in a single-stranded aptamer bounded on an electrode and exonuclease that catalyzes its hydrolysis. When the insulin from the sample is bound to the aptamer, hydrolysis does not occur and added probes can create a detectable sandwich structure (57). Sisolakova and co-authors (2020) prepared two types of modifications of screen-printed carbon electrodes. Both types were modified with a chitosan membrane containing multi-walled carbon nanotubes, the first was modified with copper nanoparticles, the second was modified with cobalt nanoparticles, and this sensor showed better analytical parameters (58). Screen-printed carbon electrodes were also used in the work of Singh (2019), where they were functionalized with multi-walled carbon nanotubes and quantum dots (59). Zhao et al (2017) (60) fabricated a molecularly imprinted electrochemical sensor based on indirect detection using potassium ferricyanide/potassium ferrocyanide as a probe was fabricated by Zhao and co-authors (2017) (60).

Khanwalker et al (2022) proposed the point of care testing device for insulin measurement. The sensor was based on an anti-insulin single-chain variable fragment (scFv) as a biosensing molecule and potassium ferricyanide as a redox probe (61).

As can be seen from the summary analytical characteristics in Table 4, insulin can be detected at picomolar and femtomolar concentrations using the proposed sensors, and this low detection limit was achieved with a probe. Sufficient sensitivity of other sensors is questionable, because in healthy individuals the blood insulin level is 3–15 mIU/l (18–90 pmol/l), according to the work of Wilcox (2005). According to the work of Linnebjerg et al (2017), the detected levels of insulin in the blood reach values between 50 and 2000 pM (62, 63). Therefore, at least picomolar concentrations should be detectable by designed sensors, if their use in blood samples is intended.

Conclusions

Non-enzymatic glucose sensors independent of pH or temperature of analysis, non-invasive glucose sensors avoiding infection and pain during sampling, wearable glucose sensors enabling all-day glucose monitoring, and non-glucose sensors corresponding to long-term glucose levels should be the future of the diagnosis and treatment of DM. However, there is still a long way to implement these sensors. Issues including low sensitivity, uneven sampling, poor resistance to impact and water of devices or interferences must be solved. On the other hand, solving these problems offers great prospects for the future diagnosis and treatment of DM.

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