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# Hypoglycemic potential of *Sargassum* spp.: A review of bioactive compounds for diabetes management

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**ABSTRACT**

Diabetes mellitus is a rapidly growing global health challenge, and the side effects of current pharmacotherapies have intensified the search for safer anti-hyperglycemic options. Brown seaweeds of the genus *Sargassum* contain diverse bioactive constituents with promising glucose-lowering activity. This review systematically evaluates the hypoglycemic effects of *Sargassum* bioactive compounds by analyzing studies retrieved from PubMed, Scopus, and Web of Science (2014–2024; OSF registration ID osf-registration-2yp8v-v1). Sixteen pre-clinical investigations that met predefined criteria were appraised with the Mixed Methods Appraisal Tool, and their data were coded and synthesized qualitatively in NVivo. Extracts from eleven *Sargassum* species lowered fasting or post-prandial glucose, enhanced insulin sensitivity, and improved lipid profiles in rodent models. Key constituents—polyphenols, terpenoids, polysaccharides, and polyunsaturated fatty acids—acted by inhibiting α-glucosidase/α-amylase, promoting GLUT4 translocation, and attenuating oxidative stress signaling. No meta-analysis was feasible because of heterogeneity in study design, and the evidence remains limited to animal models, underscoring the need for well-designed human trials and dose-response studies before pharmaceutical or nutraceutical translation.



## 1. INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder characterized by persistent hyperglycemia arising from inadequate insulin secretion, impaired insulin action, or both [1]. By 2025, global prevalence is projected to exceed 300 million cases, making DM a leading contributor to morbidity and mortality worldwide [2]. The resulting metabolic imbalance triggers lipid and protein catabolism, generating free radicals through lipid autoxidation [3] and fueling complications such as coronary heart disease, stroke, retinopathy, nephropathy, liver disorders, and peripheral neuropathy [4].

Current first-line therapies—insulin injections and oral antidiabetic drugs—are effective but often cause gastrointestinal discomfort, weight gain, or hypoglycemia and show waning efficacy over long-term use [5–7]. Consequently, there is growing interest in safer, natural anti-hyperglycemic agents.

Marine macroalgae have come into focus as reservoirs of novel bioactives. Brown seaweeds in the genus *Sargassum* are particularly rich in phlorotannins, fucoidans, terpenoids, polysaccharides, and polyunsaturated fatty acids, compounds with antioxidant, anti-inflammatory, and antidiabetic properties [8–10]. Notably, phytochemical profiles and biological potency differ markedly among *Sargassum* species, underscoring the need for species-level comparison. Advances in marine biotechnology—such as controlled aquaculture, enzyme-assisted extraction, and biorefinery platforms—could facilitate the scalable production of these metabolites for pharmaceutical development. Recent advances include enzyme-assisted deep-eutectic-solvent extraction, ultrasound-coupled pressurized liquid extraction, and integrated multitrophic aquaculture that yields *Sargassum* biomass with controlled chemotypes suitable for current Good Manufacturing Practice (cGMP) supply chains.

This review synthesizes evidence published between 2014 and 2024 on the hypoglycemic activity of *Sargassum* bioactive compounds. It evaluates dosage forms, dosing

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regimens, study duration, efficacy end-points, and mechanisms of action reported in pre-clinical models, aiming to clarify the therapeutic prospects of *Sargassum* and identify knowledge gaps for future research.

## 2. METHODOLOGY

This structured review followed the PRISMA 2020 reporting checklist and was prospectively registered in the Open Science Framework (OSF; ID osf-registration-2yp8v-v1) because PROSPERO does not currently accept animal-only reviews. Specific research questions were developed a priori, and the protocol (objectives, eligibility criteria, search strings, analysis plan) was finalized before screening began [11–14].

A comprehensive search of PubMed, Scopus, and Web of Science (2014–2024) used the string *("Sargassum") AND (bioactive OR hyperglycemi OR diabet* OR "insulin resistance" OR "fasting blood glucose" OR "blood glucose" OR "oral glucose tolerance test" OR OGTT) with English-language and primary-study filters. Records were deduplicated and then screened by title/abstract and full text against preset criteria as follows: (i) *Sargassum* intervention; (ii) *in vivo* diabetic model; and (iii) glycemic outcome. Reviews, conference papers, and book chapters were excluded.

Study quality was assessed with the Mixed Methods Appraisal Tool [15]. Because all eligible studies involved animals, risk-of-bias domains were additionally explored with the SYRCLE RoB tool; results are summarized in Supplementary Table S1. We archived the full, prospectively developed protocol—including search terms, eligibility criteria, analysis procedures, and risk-of-bias strategy—on the Open Science Framework (OSF; DOI 10.17605/OSF.IO/2YP8V) [16].

Data were extracted independently by two reviewers using a piloted spreadsheet capturing species, dose, duration, dosage form, bioactives, and mechanisms. The completed extraction file is provided as Supplementary Table S2 to enhance reproducibility.

Heterogeneity in models, doses, and outcome measures precluded quantitative pooling; therefore, findings were synthesized narratively and thematically with NVivo [17–19]. No meta-analysis was undertaken. Mechanistic themes were mapped to identify knowledge gaps and priorities for future clinical translation.

## 3. RESULTS AND DISCUSSION

### 3.1 Search and selection outcomes

Figure 1 illustrates the PRISMA 2020 flowchart, which documents the identification, screening, and inclusion of



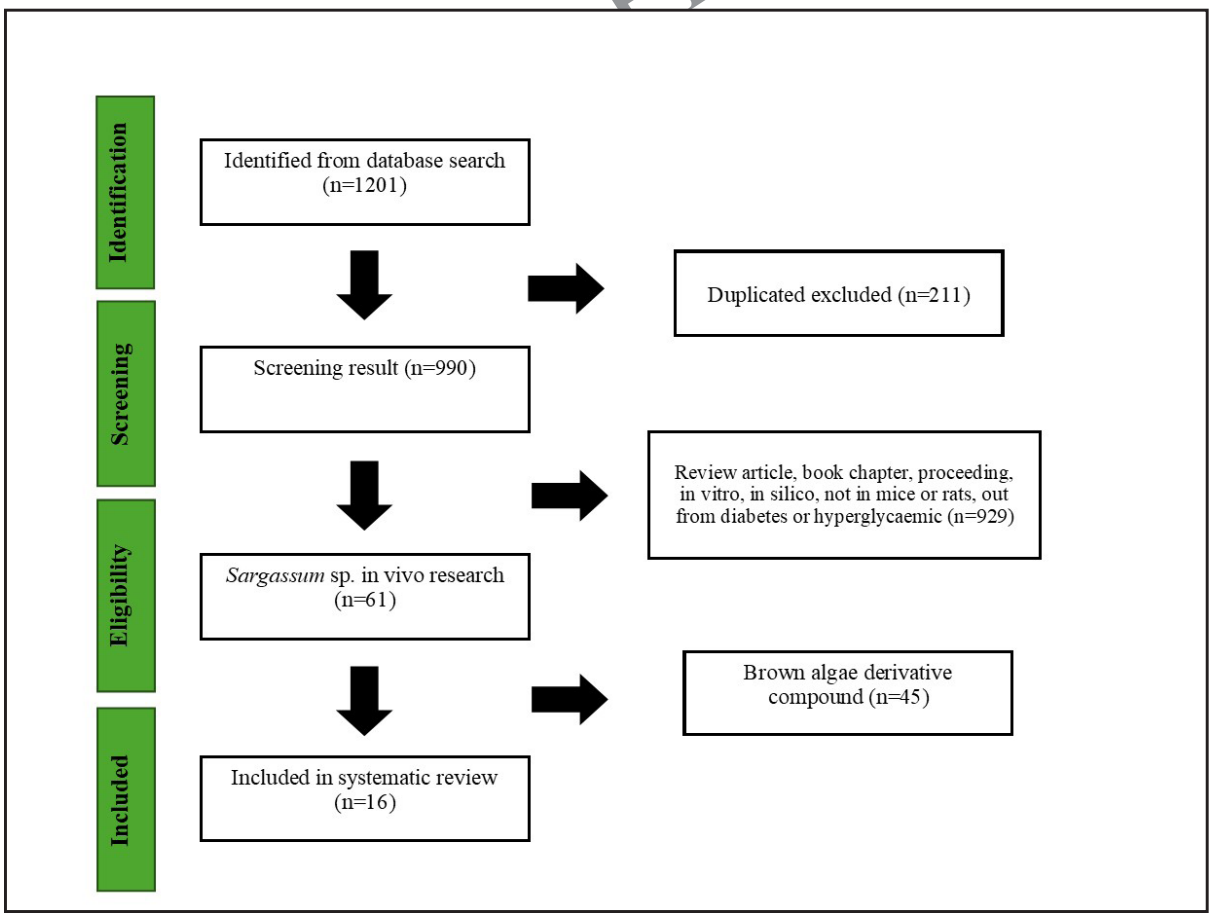


**Figure 1.** PRISMA flowchart.

studies. After deduplication, 990 records were screened; 16 met all eligibility criteria.

SYRCLE analysis revealed a generally low risk for randomization but frequent unclear or high risk for allocation concealment, housing randomization, and blinding (Supplementary Table S1), underscoring the moderate certainty of the pre-clinical evidence. The SYRCLE risk-of-bias appraisal reveals a recurring methodological weakness across the 16 pre-clinical studies: while most reports describe complete outcome data, they rarely document procedures that safeguard against selection and performance bias. Only six studies explicitly state how they generated random sequences, leaving the majority with an "unclear" judgment and raising concerns that group assignments might not have been truly random. More critically, none of the investigations describes allocation concealment or random housing practices, and the authors seldom report caregiver or outcome-assessor blinding. We rated several studies "high risk" when we could assess these latter domains, indicating that personnel likely knew the treatment assignments and that cage effects or observer expectations could have influenced results.

In contrast, attrition bias appears minimal: the reviewers judged all studies "low risk" for incomplete outcome data, suggesting that investigators limited or transparently handled sample losses and exclusions. Selective-reporting bias remains difficult to dismiss because half of the papers fail to signal whether they published all predefined outcomes, and none provides access to a pre-registered protocol. The "other bias" category likewise registers as "unclear" in every case, reflecting inadequate disclosure about funding sources, animal-housing conditions, or environmental variables that might have confounded metabolic read-outs.

These patterns point to an overall body of evidence whose certainty would fall to "moderate–low" in a GRADE framework. Therefore, the consistently favorable glucose-lowering effects attributed to *Sargassum* extracts could be exaggerated, given the plausible influence of unconcealed allocation, non-blinded assessments, and potential cage clustering. Consequently, we should interpret current findings as preliminary proof-of-concept rather than definitive demonstrations of therapeutic efficacy.

Future animal studies should adopt best-practice guidelines—transparent block randomization, sealed allocation, randomized cage placement, and blinded biochemical and histological assessments—to reduce bias and enhance reproducibility. Public registration of detailed pre-clinical protocols would also discourage selective reporting. Such methodological rigor is essential before researchers progress to human trials or seek regulatory approval for *Sargassum*-derived pharmaceutical or nutraceutical products.

### 3.2. Geographic distribution of studies

Table 1 presents the countries in which the included studies were performed; Indonesia and South Korea predominate, reflecting their extensive coastlines and established seaweed industries [20].

### 3.3. Study characteristics and outcomes

Table 2 summarizes dosage, duration, preparation type, and key findings. Across rodent models, extracts or powders from eleven *Sargassum* species consistently lowered fasting or post-prandial glucose, enhanced insulin sensitivity, and improved lipid profiles. The largest glucose reduction (−46%) was reported for a 600 mg $kg^{-1}$ methanolic extract of *Sargassum polycystum* [21], whereas the briefest intervention (120 minutes) employed MeOH 80% extract of *Sargassum boveanum* and still achieved a significant post-prandial decrement [6].

### 3.4. Categorization of mechanisms of action

To aid clarity, mechanisms were grouped into three themes:

(i) Enzymatic inhibition: α-glucosidase/α-amylase blockade by *Sargassum yezoense*, *S. boveanum*, and *Sargassum sagamianum* delays carbohydrate digestion and glucose absorption [6,24,27]. (ii) Insulin-sensitizing signaling: PI3K/Akt activation and GLUT4 translocation documented for *Sargassum horneri*, *Sargassum oligocystum*, and *Sargassum pallidum* increase peripheral glucose uptake [2,7,30].

(iii) Metabolic homeostasis and anti-oxidative modulation: reductions in Reactive oxygen species (ROS), inflammatory cytokines, or hepatic gluconeogenesis seen with *Sargassum fusiforme*, *S. horneri*, and *Sargassum coreanum* improve whole-body glycemic control [22,30,31], However, the mechanistic certainty is tempered by RoB concerns noted earlier.

### 3.5. Comparative efficacy among species

Although most species produced favorable outcomes, *S. polycystum* (ethanol/methanol extracts) and *S. oligocystum* (hydro-alcoholic extract) demonstrated the greatest combined improvements in glycaemia and β-cell histology, whereas *S. horneri* powder excelled in lipid-lowering and weight-

**Table 1.** Country of research article.

| Author | Year | Country |
|---|---|---|
| Motshakeri *et al.* [21] | 2014 | Malaysia |
| Park *et al.* [22] | 2015 | South Korea |
| Oh *et al.* [23] | 2016 | South Korea |
| Park *et al.* [24] | 2017 | South Korea |
| Akbarzadeh *et al.* [2] | 2018 | Iran |
| Firdaus and Chamidah [25] | 2018 | Indonesian |
| Gotama and Husni [26] | 2018 | Indonesian |
| Lee and Han [27] | 2018 | South Korea |
| Renitta *et al.* [28] | 2020 | India |
| Lindsey *et al.* [29] | 2021 | India |
| Murakami *et al.* [30] | 2021 | Japanese |
| Wu *et al.* [31] | 2021 | China |
| Firdaus *et al.* [32] | 2022 | Indonesian |
| Lee *et al.* [33] | 2023 | South Korea |
| Moheimanian *et al.* [6] | 2023 | Iran |
| Xie *et al.* [7] | 2023 | China |

**Table 2.** Selected studies analyzing the impact of *Sargassum* sp on diabetic *in vivo* trials.

| References | Year | Duration | Dose | Types of seaweed | Dosage form | Effectiveness | Types of bioactive compounds | Mechanism |
|---|---|---|---|---|---|---|---|---|
| Motshakeri *et al.* [21] | 2014 | 22 days | 300 mg/kg | *Sargassum polycystum* | Ethanol and water extracts | Glucose reduction; pancreatic, hepatic and renal histopathological improvement | Natural antioxidants | Pancreatic protection and restoration; hepatic and renal repair; islet regeneration |
| Park *et al.* [22] | 2015 | 42 days | 0.5% | *Sargassum coreanum* | Extract | Reductions in blood glucose, plasma insulin and HOMA-IR; decreases in hepatic G6Pase and PEPCK activities | Phycocolloids, pigments, polyphenol compounds (e.g., phlorotannin) | Glucokinase activation; suppression of hepatic gluconeogenesis; lipid-profile improvement |
| Oh *et al.* [23] | 2016 | 112 days | 5% | *Sargassum fulvellum* | Freeze-dried powder | Insulin-sensitivity enhancement; glucose reduction; attenuation of crown-like-structure formation; cytokine reduction | Proteins, vitamins, minerals, fiber, PUFAs, bioactive components, polyphenols, polysaccharides | Inflammatory-signal inhibition; mitigation of HFD-induced metabolic complications |
| Park *et al.* [24] | 2017 | 14 days | 300 mg/kg | *Sargassum yezoense* | Extract | Strong α-glucosidase and α-amylase inhibition; post-prandial glucose reduction; lower $IC_{50}$ relative to acarbose | Sargaquinoic acid, sargahydroquinoic acid, plastoquinones | Delayed glucose absorption via carbohydrate-hydrolase blockade; suppression of starch-derived glucose production |
| Akbarzadeh *et al.* [2] | 2018 | 30 days | 150–300 mg/kg | *Sargassum oligocystum* | Hydro alcoholic extracts | Fasting-glucose and triglyceride reduction; HOMA-IR reduction; HOMA-B increase; β-cell regeneration | Pigments, fucoidans, polyphenols | Reactive-oxygen-species inhibition; adipogenesis suppression; α-glucosidase inhibition |
| Firdaus and Chamidah [25] | 2018 | 45 days | 600 mg/kg | *Sargassum polycystum* | Methanol extract | Blood-glucose reduction; HbA1c reduction | Steroids, alkaloids, phenolics, flavonoids, saponins, sterols | Phenolic insulin-mimetic action; hemoglobin-glycation inhibition |
| Gotama *et al.* [26] | 2018 | 15 days | 200–400 mg/kg | *Sargassum hystrix* | Ethanol extract | Reductions in blood glucose, triglycerides and cholesterol; pancreatic-cell preservation | Antioxidant | α-Glucosidase inhibition; insulin-mimetic activity; pancreatic-cell repair |
| Lee and Han [27] | 2018 | 14 days | 300 mg/kg | *Sargassum sagamianum* | Extract | High α-glucosidase and α-amylase inhibition; post-prandial glucose reduction | Plastoquinone, phlorotannin, farnesyl acetone derivatives, polyphenols | Carbohydrate-digestive-enzyme inhibition; delay of dietary-carbohydrate absorption |
| Renitta *et al.* [28] | 2020 | 15 days | 250 mg/kg | *Sargassum wightii* | Methanol extract | Reductions in blood glucose, total cholesterol, LDL-C, VLDL-C and triglycerides; HDL-C increase | Protein, vitamins, soluble fiber, PUFAs, minerals, antioxidants, fucoidans, phycocolloids, phlorotannins, alginic acid, fucosterol, fucoxanthin | Phlorotannin-mediated lipid and glucose regulation |
| Lindsey *et al.* [29] | 2021 | 15 days | 100–500 mg/kg | *Sargassum tenerrimum* | Methanol extract | Body-weight and HDL-C increase; reductions in total cholesterol, VLDL-C, LDL-C, triglycerides, SGOT, SGPT, creatinine and urea | Phlorotannin | Inhibition of hyperglycemia-related metabolic enzymes |



***(Continued)***

| References | Year | Duration | Dose | Types of seaweed | Dosage form | Effectiveness | Types of bioactive compounds | Mechanism |
|---|---|---|---|---|---|---|---|---|
| Murakami *et al.* [30] | 2021 | 91 days | 2%–6% | *Sargassum horneri* | Freeze-dried powder | Suppression of weight gain and fat accumulation; serum-glucose reduction; increased fecal triglyceride and polysaccharide excretion | Polyphenols, carotenoids, fucoidans, fucostinates, alginates | Pancreatic-lipase inhibition; fucoidan and fucoxanthin bioactivity enhancement |
| Wu *et al.* [31] | 2021 | 28 days | 100 mg/kg | *Sargassum fusiforme* | Ethanol extract | Reductions in food/water intake and fasting glucose; improved glucose tolerance and lipid profile; decreased epididymal-fat deposition and cardiac/hepatic pathology; enrichment of beneficial gut bacteria | Polysaccharides, polyphenols, phycobilin, carotenoids, vitamins, amino acids, hydroxyphenyl acetic acid | Branched- and aromatic-amino-acid reduction; hydroxyphenyl-acetic-acid elevation; gut-microbiota modulation |
| Muhamad *et al.* [32] | 2022 | 45 days | 4 ml/kg | *Sargassum oligocystum* | Extract | Blood-glucose reduction; glucose-uptake enhancement | Amino acids, terpenes, terpenoids, indole, caprolactam, sulfonamides, nucleotides, carboxylic acid derivatives, cinnamic acid derivatives, flavonoid derivatives, polyphenols | PTP1B inhibition; PI3K/Akt-pathway activation |
| Lee *et al.* [33] | 2023 | 42 days | 500 mg/kg | *Sargassum horneri* | Extract | Reactive-oxygen-species reduction; increased glucose uptake and glycogen content; IRS-1/Akt and GLUT4 expression enhancement | Neophytadiene, hexadecenoic acid, and ethyl ester | GSK-3β-mRNA suppression; intracellular-ROS reduction; GLUT4-translocation enhancement |
| Moheimanian *et al.* [6] | 2023 | 120 min | 30 mg/kg | *Sargassum boveanum* | MeOH Extract 80% | Post-prandial glucose reduction in STZ-induced diabetic mice | Polyphenols, PUFAs, dietary fiber, fucoxanthin | Dietary-carbohydrate absorption inhibition; competitive α-glucosidase inhibition |
| Xie *et al.* [7] | 2023 | 28 days | 50–250 mg/kg | *Sargassum pallidum* | Powder | Reductions in hyperglycemia, insulin resistance, hyperlipidemia, oxidative stress and hepatic-pancreatic damage; intestinal-function restoration; enrichment of beneficial microbiota | Phenolic (6-gingerol, quercetin-3-O-glucuronide, kuraridine, n-hexacosyl caffeatehexose) | PI3K/Akt/FOXO1/G6Pase/GLUT2 modulation; fatty-acid-synthesis inhibition via FAS and ACC-1 down-regulation; antioxidant-enzyme enhancement; gluconeogenesis improvement; unsaturated-fatty-acid-biosynthesis modulation |



control parameters. These inter-specific differences likely reflect variable phlorotannin and fucoidan yields; advances in enzyme-assisted extraction and controlled mariculture could optimize the production of the most potent chemotypes for drug development.

### 3.6. Clinical and regulatory perspective

Compared with metformin, the benchmark first-line oral drug, *Sargassum* extracts achieved comparable glucose reductions in animals without reported hypoglycemic crises or gastrointestinal distress. However, translation is

constrained by the absence of human trials, uncertain dose equivalence, and regulatory hurdles in standardizing complex mixtures. A pragmatic roadmap would involve: (i) establishing cGMP extraction with validated markers (e.g., fucoxanthin, phlorotannin); (ii) submitting an investigational new drug dossier for a standardized extract; (iii) completing Phase I safety/pharmacokinetic studies; (iv) conducting adaptive Phase II/III efficacy trials; and (v) pursuing either botanical-drug (US FDA) or phytopharmaceutical (EMA/ASEAN) registration pathways.

### 3.7. Limitations

Evidence is limited to short-term pre-clinical (animal-only) studies with heterogeneous designs, precluding meta-analysis and preventing formal GRADE certainty grading. Future work should include dose-response investigations, chronic interventions, and well-powered clinical trials.

## 4. CONCLUSION

Based on the evidence synthesized in this review, extracts or powders from several *Sargassum* species consistently improved glycemic and lipid endpoints in rodent models, confirming their promise as natural anti-hyperglycemic agents. The active constituents—polyphenols, terpenoids, alkaloids, steroids, flavonoids, carotenoids, polysaccharides, and polyunsaturated fatty acids—act through complementary pathways, including α-glucosidase/α-amylase inhibition, PI3K/Akt-GLUT4 signaling, antioxidant modulation, and gut-microbiota remodeling. However, the current evidence base is limited to heterogeneous short-term animal studies, and no quantitative pooling was feasible; hence, translational certainty remains low. The well-designed human trials, dose-response and pharmacokinetic studies, and GMP-compliant standardization of key marker compounds are critical next steps before *Sargassum* bioactives can advance toward pharmaceutical or nutraceutical approval.

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## 6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

## 9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## 10. DATA AVAILABILITY

All supplementary tables and extracted datasets are available at OSF (https://10.17605/osf.io/2yp8v).

## 11. PUBLISHER'S NOTE

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## 12. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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## SUPPLEMENTARY MATERIAL

The supplementary material can be accessed at the link here: [https://japsonline.com/admin/php/uploadss/4683_pdf.pdf]